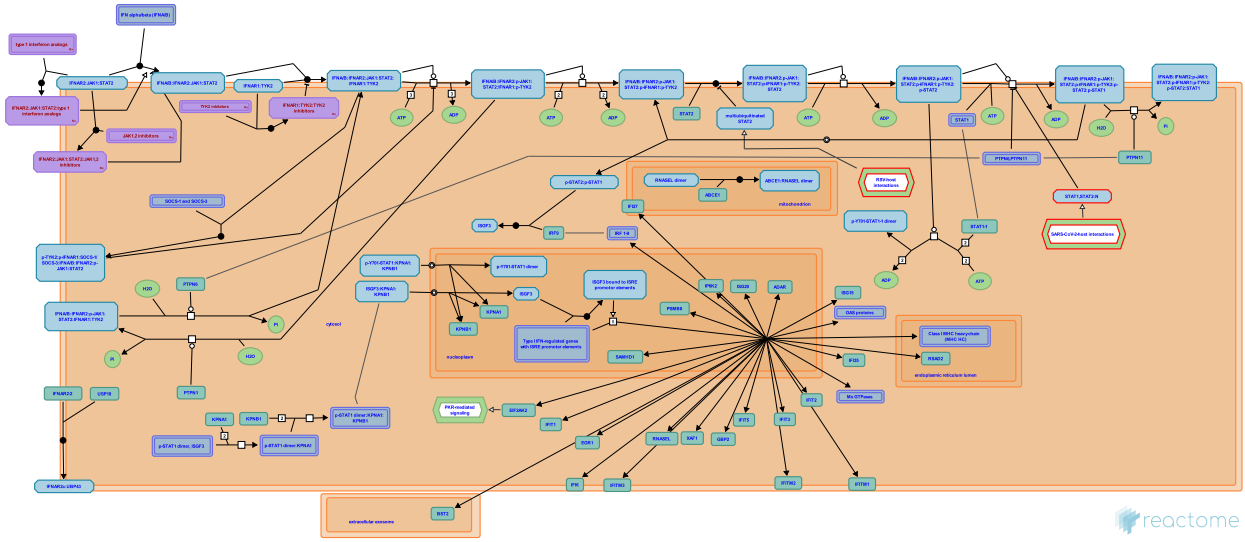
Interferon alpha/beta signaling



Abdul-Sater, AA., Bergeron, HC., D'Eustachio, P., Garapati, P V., Huddart, R., Jassal, B., Matthews, L., Messina, F., Palazzo, AF., Schindler, C., Shamovsky, V., Shen, Q., Shoichet, BK., Stephan, R.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

17/05/2024

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

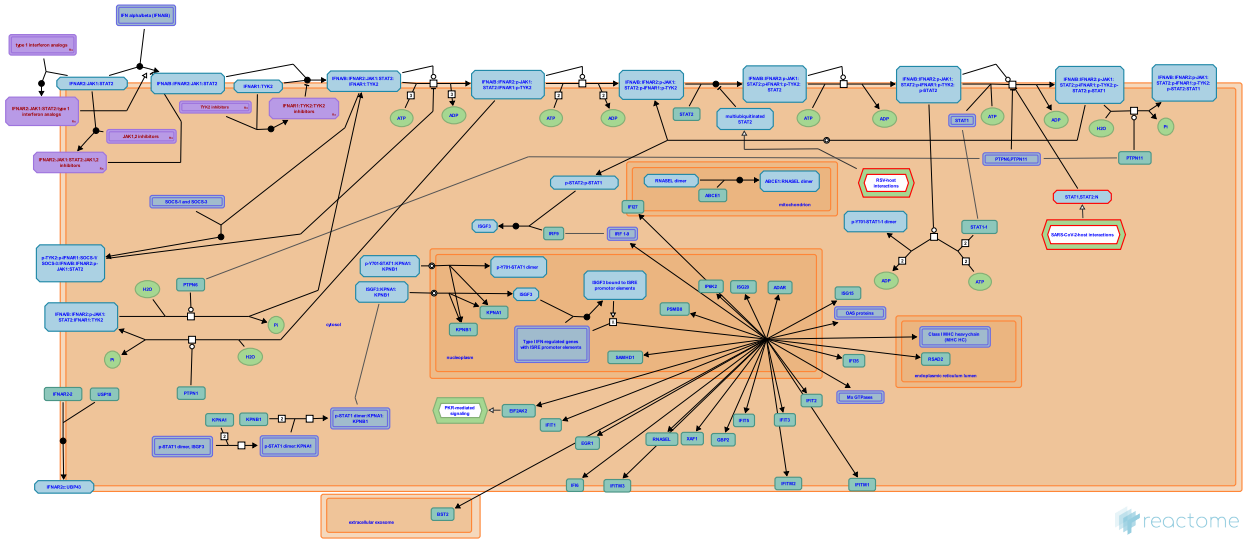
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

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

Gupta, S., Greenlund, AC., Krolewski, JJ., Yan, H., Schreiber, RD., Schindler, CW. 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. ↗

Pellegrini, S., Piehler, J., Schreiber, G., Uzé, G. (2007). The receptor of the type I interferon family. *Curr Top Microbiol Immunol, 316*, 71-95. ↗

Gauzzi, MC., Pellegrini, S., Velazquez, L., McKendry, R., Fellous, M., Mogensen, KE. (1996). Interferon-alpha-dependent activation of Tyk2 requires phosphorylation of positive regulatory tyrosines by another kinase. *J Biol Chem, 271*, 20494-500. ↗

Stark, GR., Darnell JE, Jr., Qureshi, S., Li, X., Leung, S. (1996). Formation of STAT1-STAT2 heterodimers and their role in the activation of IRF-1 gene transcription by interferon-alpha. *J Biol Chem, 271*, 5790-4. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

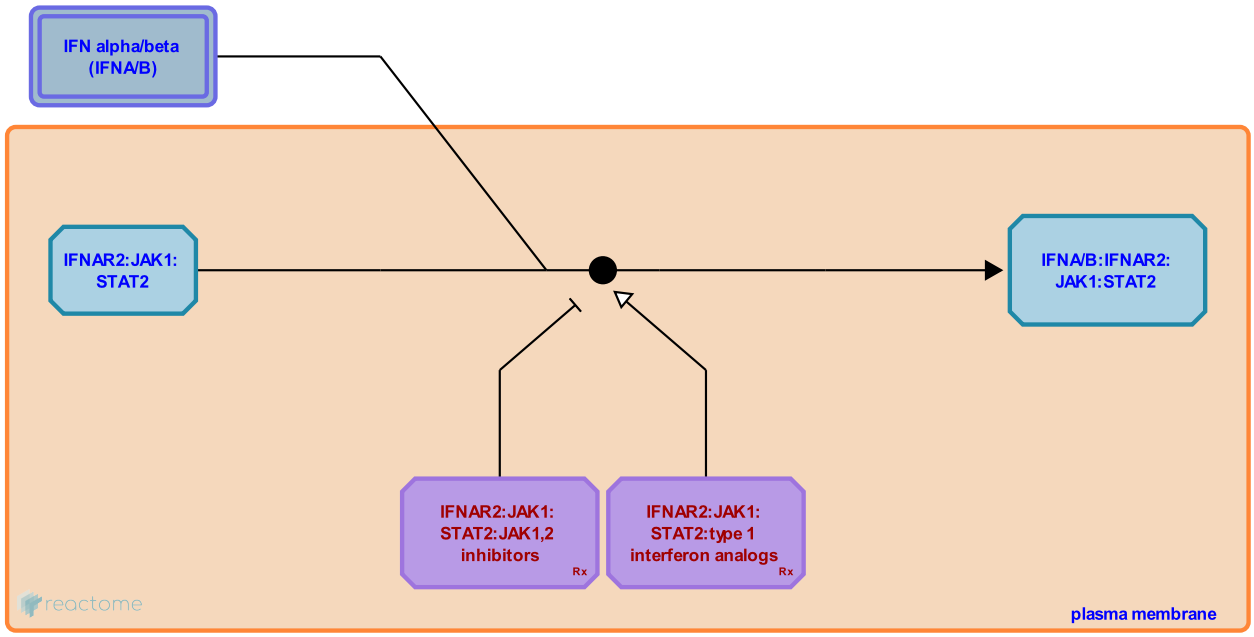
IFN alpha/beta binds to IFNAR2 ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909720

Type: binding

Compartments: plasma membrane, extracellular region



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

Literature references

Piehler, J., Gavutis, M., Lata, S., Lamken, P., Müller, P. (2005). Lateral ligand-receptor interactions on membranes probed by simultaneous fluorescence-interference detection. *Biophys J, 88*, 4289-302. ↗

Krolewski, J., Colamonici, OR., Yan, H., Pitha, P., Fish, E., Platanias, LC. et al. (1997). A region of the beta subunit of the interferon alpha receptor different from box 1 interacts with Jak1 and is sufficient to activate the Jak-Stat pathway and induce an antiviral state. *J Biol Chem, 272*, 26388-93. ↗

Schreiber, G., Anglister, J., Levy, R., Quadt, SR., Chill, JH. (2003). The human type I interferon receptor: NMR structure reveals the molecular basis of ligand binding. *Structure, 11*, 791-802. ↗

Stark, GR., Kerr, IM., Li, X., Leung, S. (1997). Functional subdomains of STAT2 required for preassociation with the alpha interferon receptor and for signaling. *Mol Cell Biol, 17*, 2048-56. ↗

Pellegrini, S., Piehler, J., Schreiber, G., Uzé, G. (2007). The receptor of the type I interferon family. *Curr Top Microbiol Immunol, 316*, 71-95. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

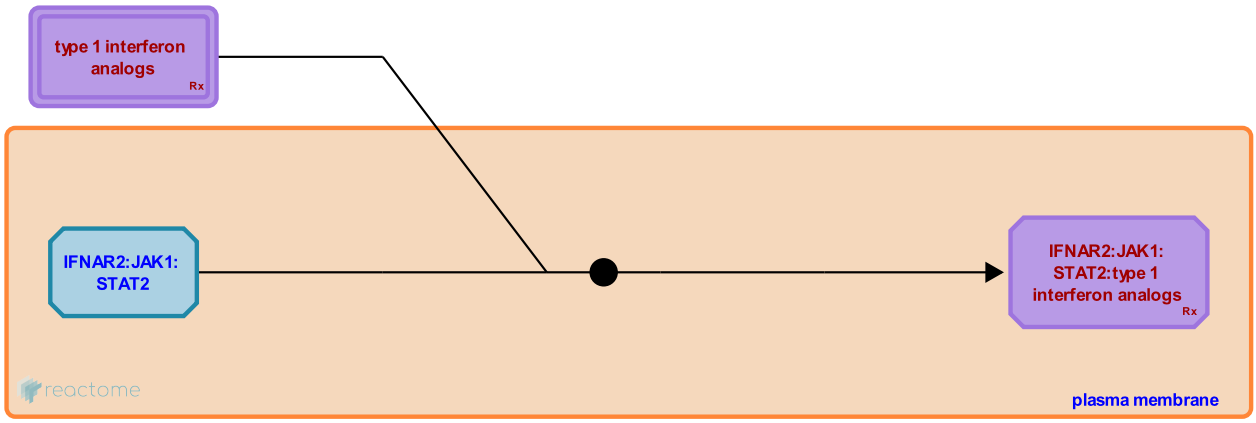
IFNAR2:JAK1:STAT2 binds type 1 interferon analogs ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-9696179

Type: binding

Compartments: plasma membrane, extracellular region



Natural ligands of the IFNAR1/2 receptor include interferon beta (IFNB), interferon alpha (IFNA) and interferon kappa (IFNK, also called IFN-epsilon), with binding affinity to the receptor decreasing in that order. However, weaker binding still triggers the signal, but differs in the pathways that are activated. Specifically, the antiviral response is always triggered but an additional antiproliferative program appears to require stronger binding like that from IFNB (Schreiber, 2020). Recombinant interferon alpha and beta, and their pegylated versions (peginterferon-alfa and peginterferon-beta) are widely applied in cancer, multiple sclerosis and viral infections.

The type I interferon beta (IFNB) is a key modulator of the immune defence against viruses. SARS-CoV-2, the coronavirus that causes Covid-19, appears to suppress production of types I and III IFNs as part of its strategy to evade immune detection and destruction (Hadjadj et al. 2020, Blanco-Melo et al. 2020). Administering recombinant human IFNB1 is suggested to reactivate the anti-viral immune response against SARS-CoV-2 (Davoudi-Monfared et al. 2020). In a small trial, direct lung delivery via a nebuliser showed Covid-19 patients were more than twice as likely to recover from the disease as those on placebo (Monk et al, 2021). In another small trial, time to clinical improvement in the group receiving IFNB1b was significantly shorter than the control group (Rahmani et al, 2020).

The recombinant human interferons IFNB1a and INFB1b are approved drugs for the treatment of multiple sclerosis (Schwid & Panitch 2007, Comi et al. 2001, Freedman 2014), so safety has been established. At the moment 23 trials with IFNB1A for the treatment of COVID-19 are underway, 7 of them using inhaled application.

IFNA is used in antiviral therapy, mostly for treating hepatitis B and hepatitis C, often in combination with other antiviral drugs. In one small uncontrolled COVID-19 trial, nebulized IFN-α2b had positive effects on virus load and blood markers (Zhou et al, 2020).

In addition to recombinant and pegylated IFN with an amino acid sequence nearly identical to wild-type, there have been attempts to optimize binding properties by scrambling the wild-type sequence and picking versions out of the mix that show an improvement. One such product, novaferon was approved in China as cancer treatment, and in a randomized, open-label, parallel-group trial it showed antiviral effects in COVID-19 patients (Zheng et al, 2020). Further trials are underway (NCT04669015, NCT04708158).

Literature references

Wei, XS., Shannon, CP., Kollmann, TR., Xiang, X., Zhou, Q., Tebbutt, SJ. et al. (2020). Corrigendum: Interferon-α2b Treatment for COVID-19. *Front Immunol, 11*, 615275. ↗

Zarin, P., MacArthur, MR., He, X., Xiang, X., Zhou, Q., Wang, ZH. et al. (2020). Interferon-α2b Treatment for COVID-19 Is Associated with Improvements in Lung Abnormalities. *Viruses, 13*. ↗

Barkhof, F., Comi, G., Hommes, OR., Sørensen, PS., Early Treatment of Multiple Sclerosis Study Group, -., Edan, G. et al. (2001). Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet, 357*, 1576-82. ↗

Xie, Y., Niu, P., Zheng, F., Zuo, Q., Xu, Y., Ye, F. et al. (2020). SARS-CoV-2 clearance in COVID-19 patients with Nova-feron treatment: A randomized, open-label, parallel-group trial. *Int J Infect Dis, 99*, 84-91. ↗

Kazemzadeh, H., Hajiabdolbaghi, M., Abbasian, L., Khalili, H., Yekaninejad, MS., Salehi, M. et al. (2020). Efficacy and safety of interferon β-1a in treatment of severe COVID-19: A randomized clinical trial. *Antimicrob. Agents Chemother.*. ↗

Editions

2020-07-20	Authored, Edited	Jassal, B.
2021-06-16	Revised	Stephan, R.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

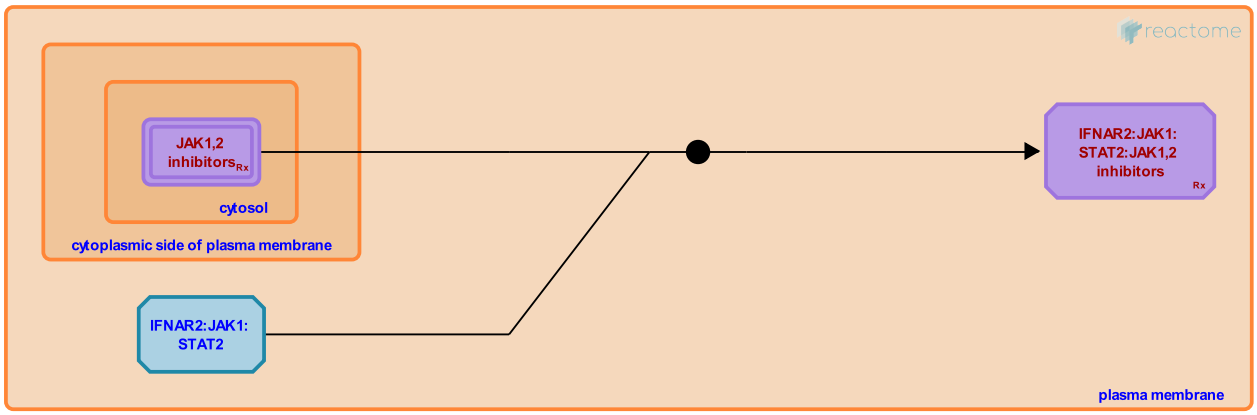
IFNAR2:JAK1:STAT2 binds JAK1,2 inhibitors ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-9678935

Type: binding

Compartments: plasma membrane, cytosol



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. JAK1 binds to and is inhibited by several small molecule drugs (Clark et al. 2014, Fridman et al. 2010). Drugs that inhibit these kinases such as baricitinib, tofacitinib, delgocitinib 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

Doi, S., Shiozaki, M., Orita, T., Yamamoto, H., Hase, Y., Hara, Y. et al. (2020). Discovery of a Janus Kinase Inhibitor Bearing a Highly Three-Dimensional Spiro Scaffold: JTE-052 (Delgocitinib) as a New Dermatological Agent to Treat Inflammatory Skin Disorders. *J Med Chem, 63*, 7163-7185. ↗

Clark, JD., Telliez, JB., Flanagan, ME. (2014). Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. *J. Med. Chem., 57*, 5023-38. ↗

Li, J., Quintás-Cardama, A., Rupar, M., Manshouri, T., Kantarjian, H., Burn, T. et al. (2010). Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms. *Blood, 115*, 3109-17. ↗

Favata, MF., Shi, J., Yeleswaram, S., Li, J., Metcalf, B., Wen, X. et al. (2010). Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J. Immunol., 184*, 5298-307. ↗

Editions

2020-03-23	Authored, Edited	Jassal, B.
2020-05-14	Reviewed	Shoichet, BK.

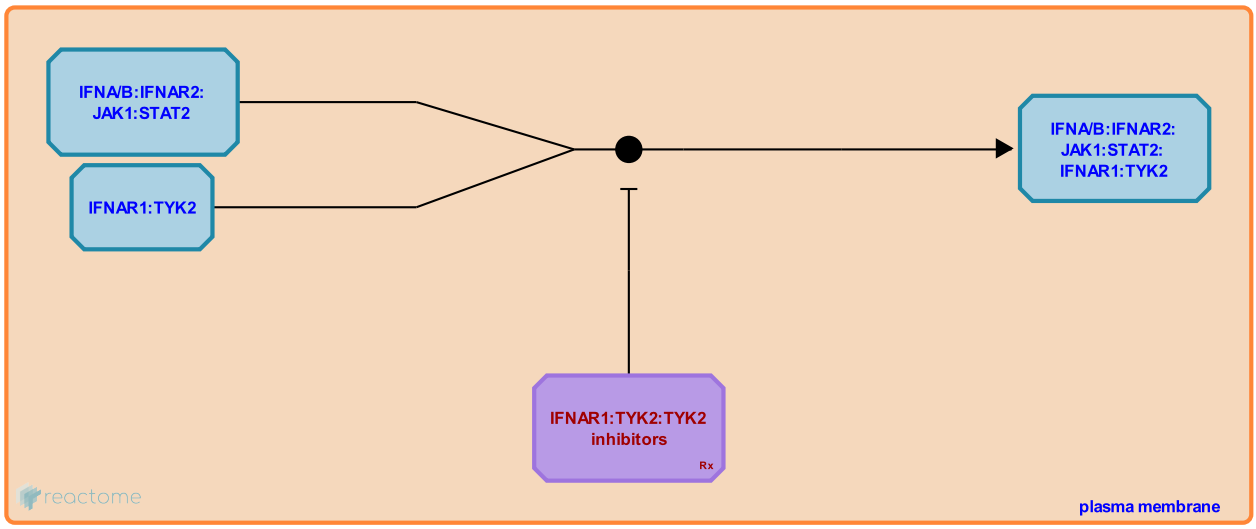
Recruitment of IFNAR1 ↗

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 (IFNAR2:IFNA/B: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

Jaitin, DA., Schreiber, G., Roisman, LC., Baker, DP. (2005). Mutational analysis of the IFNAR1 binding site on IFNalpha2 reveals the architecture of a weak ligand-receptor binding-site. *J Mol Biol, 353*, 271-81. ↗

Sempé, P., Gallet, X., Nardeux, PC., Guymarho, J., Eid, P., Tovey, MG. et al. (2004). Identification of residues of the IFNAR1 chain of the type I human interferon receptor critical for ligand binding and biological activity. *Biochemistry, 43*, 12498-512. ↗

Pellegrini, S., Piehler, J., Schreiber, G., Uzé, G. (2007). The receptor of the type I interferon family. *Curr Top Microbiol Immunol, 316*, 71-95. ↗

Piehler, J., Gavutis, M., Lata, S., Lamken, P. (2004). Ligand-induced assembling of the type I interferon receptor on supported lipid bilayers. *J Mol Biol, 341*, 303-18. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

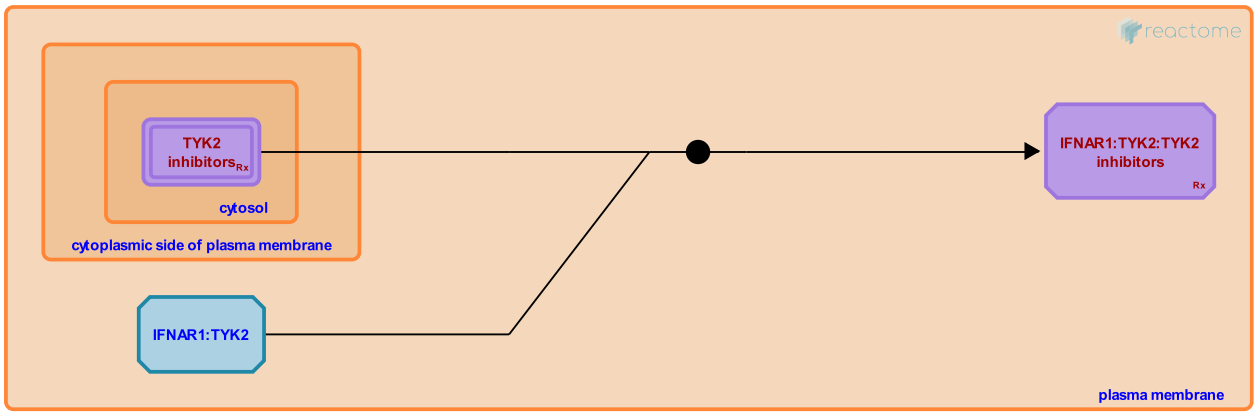
IFNAR1:TYK2 binds TYK2 inhibitors ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-9678737

Type: binding

Compartments: plasma membrane, cytosol



Non-receptor tyrosine-protein kinase TYK2 binds and is inhibited by several small molecule drugs (Clark et al. 2014, Gibbons et al. 2012). TYK2 is related to the Janus kinases (JAKs) 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 are thus plausible candidates for treatment of severe host inflammatory reactions to viral infection (Richardson et al. 2020, Stebbing et al. 2020).

Literature references

Clark, JD., Telliez, JB., Flanagan, ME. (2014). Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. *J. Med. Chem., 57*, 5023-38. ↗

Oechsle, O., Phelan, A., Tucker, C., Richardson, P., Stebbing, J., Smith, D. et al. (2020). COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis, 20*, 400-402. ↗

Chang, C., Siu, M., Murray, J., Sampath, D., Rawson, T., Ultsch, M. et al. (2012). Discovery of potent and selective pyrazolopyrimidine janus kinase 2 inhibitors. *J. Med. Chem., 55*, 10090-107. ↗

Oechsle, O., Phelan, A., Tucker, C., Stebbing, J., Richardson, P., Smith, D. et al. (2020). Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet, 395*, e30-e31. ↗

Editions

2020-03-23	Authored, Edited	Jassal, B.
2020-05-14	Reviewed	Shoichet, BK.

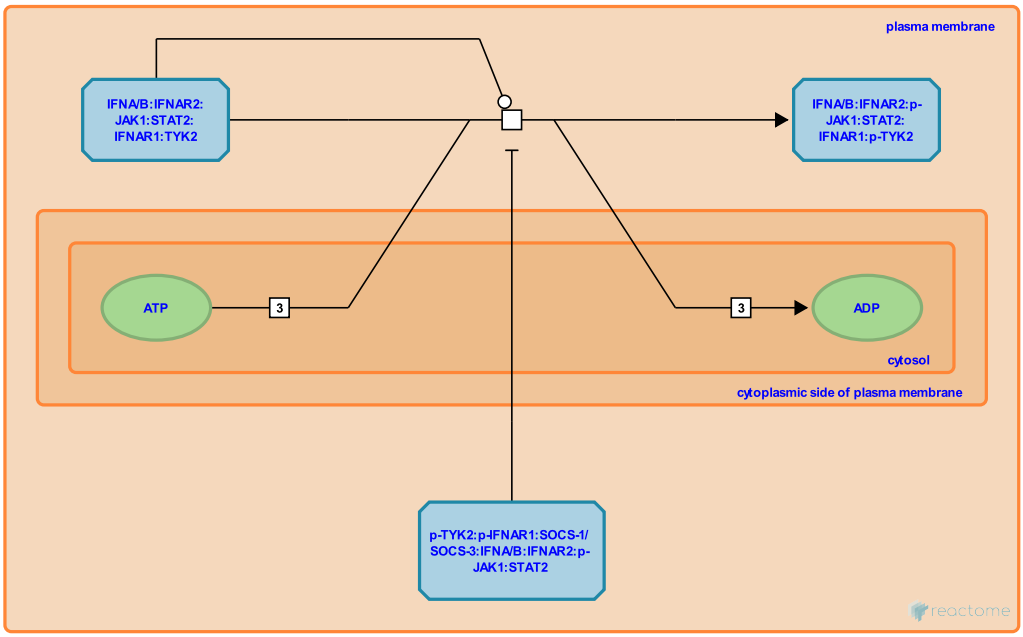
Activation of JAK kinases ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909729

Type: transition

Compartments: plasma membrane, cytosol



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 with in 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

Krolewski, J., Colamonici, OR., Yan, H., Pitha, P., Fish, E., Platanias, LC. et al. (1997). A region of the beta subunit of the interferon alpha receptor different from box 1 interacts with Jak1 and is sufficient to activate the Jak-Stat pathway and induce an antiviral state. *J Biol Chem, 272*, 26388-93. ↗

Gauzzi, MC., Pellegrini, S., Velazquez, L., McKendry, R., Fellous, M., Mogensen, KE. (1996). Interferon-alpha-dependent activation of Tyk2 requires phosphorylation of positive regulatory tyrosines by another kinase. *J Biol Chem, 271*, 20494-500. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

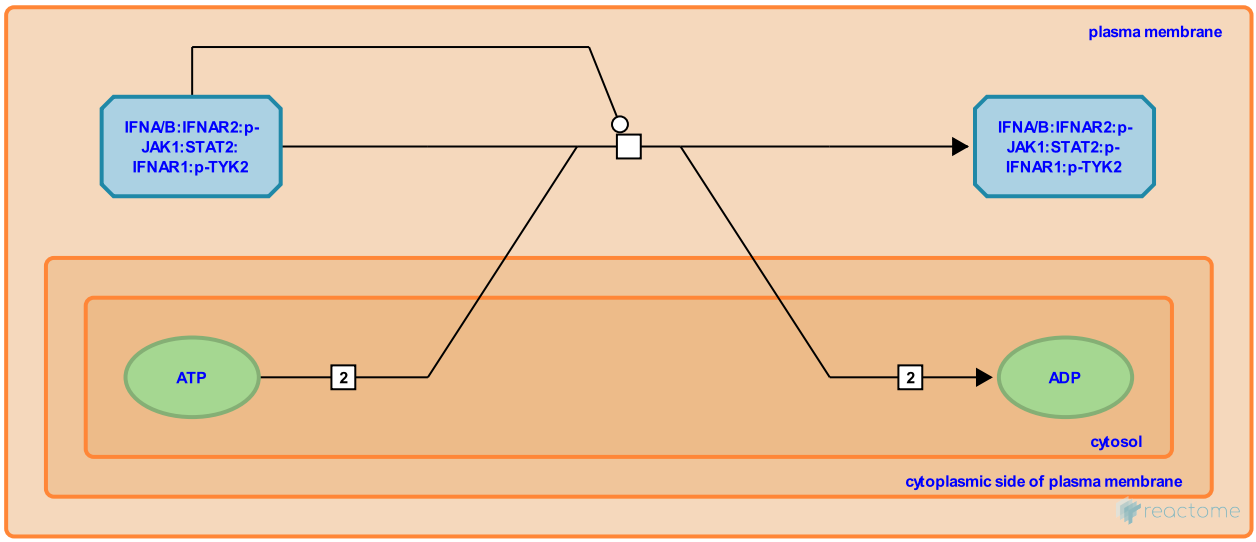
Phosphorylation of INFAR1 by TYK2 ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909730

Type: transition

Compartments: plasma membrane, cytosol



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

Literature references

Krolewski, J., Yan, H., Colamonici, O., Handa, R., Witte, M., Smalley, D. et al. (1994). Direct binding to and tyrosine phosphorylation of the alpha subunit of the type I interferon receptor by p135tyk2 tyrosine kinase. *Mol Cell Biol, 14*, 8133-42. ↗

Gupta, S., Greenlund, AC., Krolewski, JJ., Yan, H., Schreiber, RD., Schindler, CW. 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. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

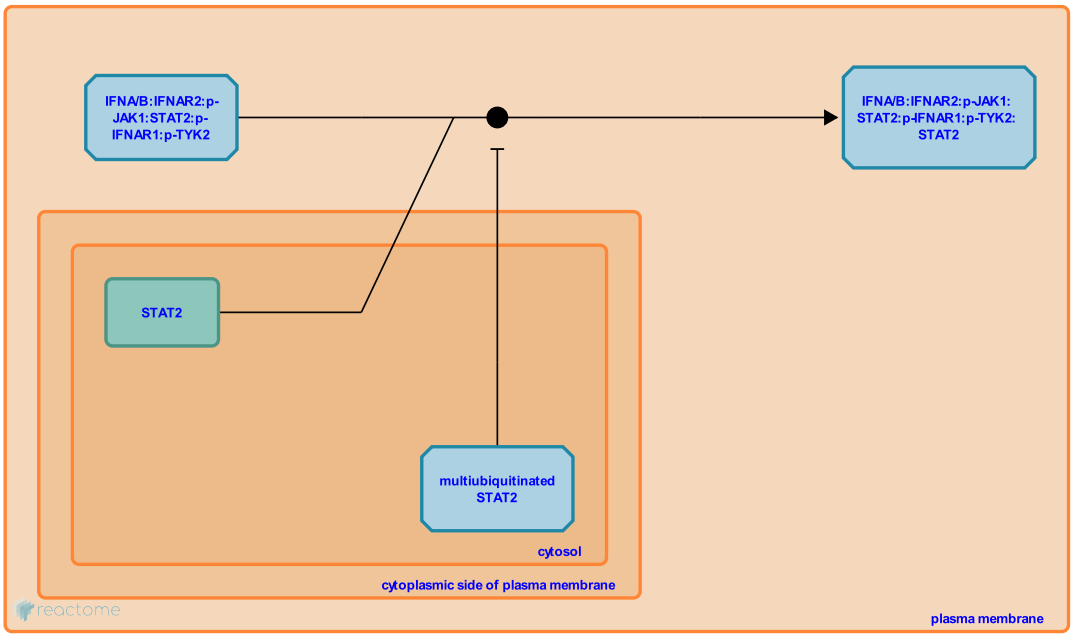
Recruitment of STAT2 to p-IFNAR1 ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909719

Type: binding

Compartments: plasma membrane, cytosol



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 (Yan et al, 1996). Infection by human respiratory syncytial virus (hRSV) leads to loss of STAT2 by ubiquitination, catalyzed by a hRSV NS1 complex with elongin C (ELOC) and cullin-5 (CUL5) acting as an E3 ubiquitin ligase, and subsequent proteasomal STAT2 degradation (Elliott et al, 2007).

Preceded by: Phosphorylation of INFAR1 by TYK2

Followed by: Phosphorylation of STAT2

Literature references

Power, UF., Johnston, JA., Touzelet, O., Stevenson, NJ., Elliott, J., Boyd, CR. et al. (2007). Respiratory syncytial virus NS1 protein degrades STAT2 by using the Elongin-Cullin E3 ligase. *J Virol, 81*, 3428-36. ↗

Gupta, S., Greenlund, AC., Krolewski, JJ., Yan, H., Schreiber, RD., Schindler, CW. 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. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.
2023-11-03	Reviewed	Bergeron, HC.

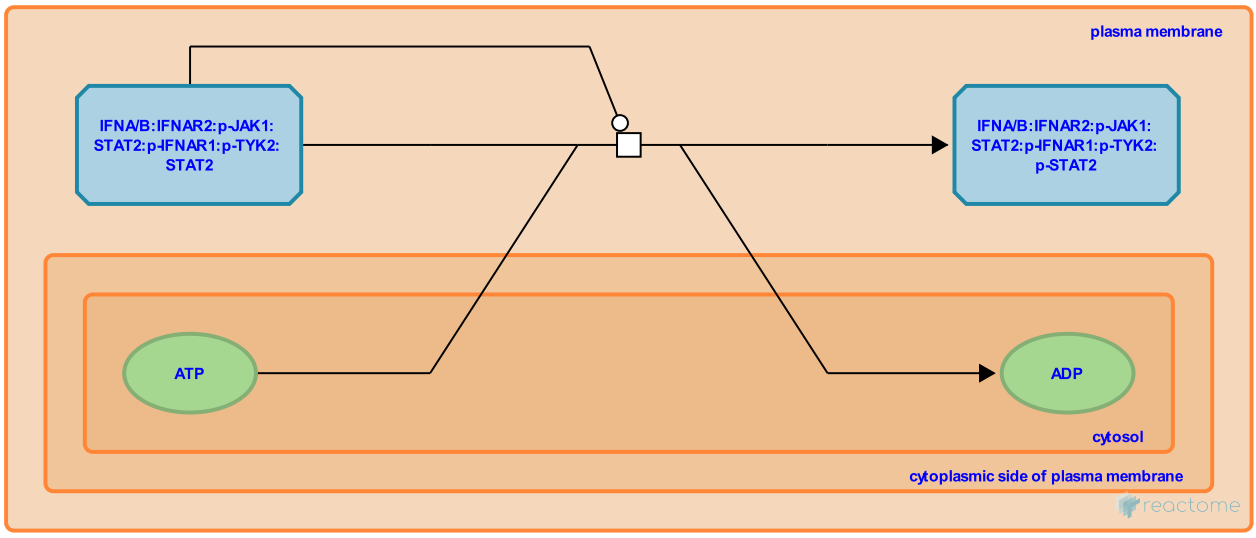
Phosphorylation of STAT2 ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909732

Type: transition

Compartments: plasma membrane, cytosol



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

Geiger, TR., Martin, JM. (2006). The Epstein-Barr virus-encoded LMP-1 oncoprotein negatively affects Tyk2 phosphorylation and interferon signaling in human B cells. *J Virol, 80*, 11638-50. ↗

Fish, EN., Leaman, DW., Rani, MR., Ransohoff, RM., Croze, E., Wolfman, A. et al. (1999). Catalytically active TYK2 is essential for interferon-beta-mediated phosphorylation of STAT3 and interferon-alpha receptor-1 (IFNAR-1) but not for activation of phosphoinositol 3-kinase. *J Biol Chem, 274*, 32507-11. ↗

Horvath, CM., Stark, GR., Darnell JE, Jr., Kerr, IM., Improta, T., Schindler, C. (1994). Transcription factor ISGF-3 formation requires phosphorylated Stat91 protein, but Stat113 protein is phosphorylated independently of Stat91 protein. *Proc Natl Acad Sci U S A, 91*, 4776-80. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

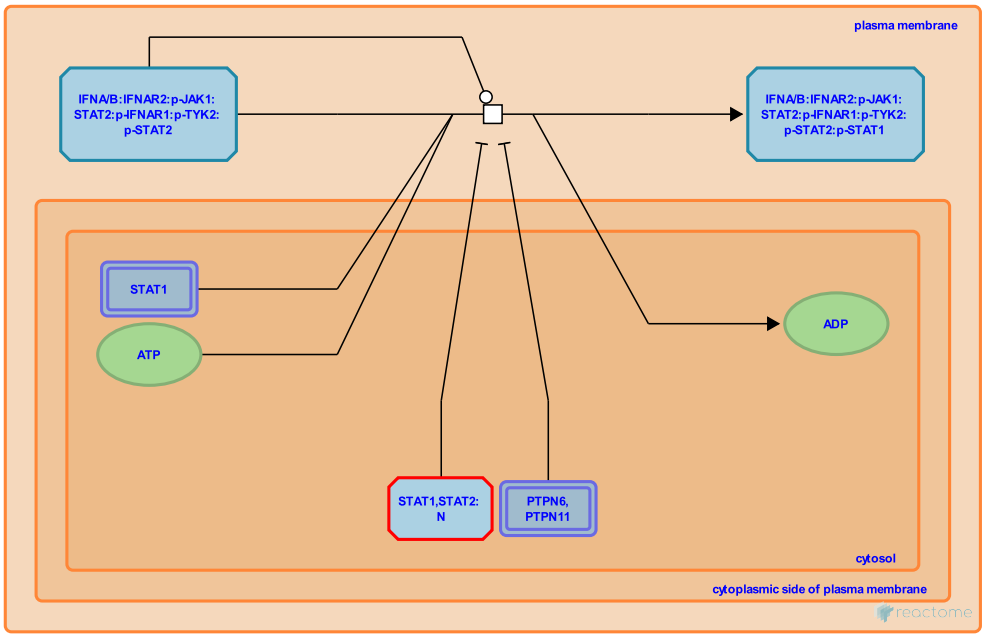
Phosphorylation of STAT1 ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909726

Type: transition

Compartments: plasma membrane, cytosol



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 phosporylated 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).
SARS-CoV-2 nucleoprotein (N) binds to both STAT1 and STAT2, prevents their phosphorylation, and suppresses their nuclear translocation induced by IFN (Mu J et al. 2020).
Protein tyrosine phosphatases SHP-1 and SHP-2 dephosphorylate JAK1 and STAT1 and suppress their signaling.

Preceded by: Phosphorylation of STAT2

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

Literature references

David, M., Mowen, K. (2000). Regulation of STAT1 nuclear export by Jak1. *Mol Cell Biol, 20*, 7273-81. ↗

Witthuhn, BA., Barbieri, G., Ziemiecki, A., Briscoe, J., Harpur, AG., Laxton, C. et al. (1993). The protein tyrosine kinase JAK1 complements defects in interferon-alpha/beta and -gamma signal transduction. *Nature, 366*, 129-35. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.
2022-02-18	Reviewed	Messina, F.

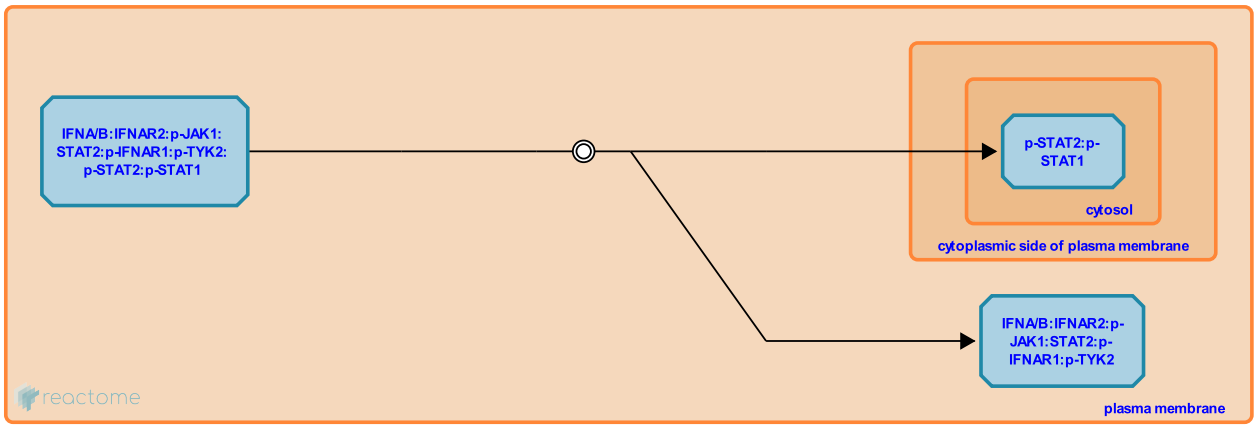
Release of p-STAT2:p-STAT1 dimer ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909722

Type: dissociation

Compartments: plasma membrane, cytosol



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

Literature references

Szweykowska-Kulinska, Z., Wesoly, J., Bluyssen, HA. (2007). STAT activation and differential complex formation dictate selectivity of interferon responses. *Acta Biochim Pol, 54*, 27-38. ↗

Stark, GR., Darnell JE, Jr., Qureshi, S., Li, X., Leung, S. (1996). Formation of STAT1-STAT2 heterodimers and their role in the activation of IRF-1 gene transcription by interferon-alpha. *J Biol Chem, 271*, 5790-4. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

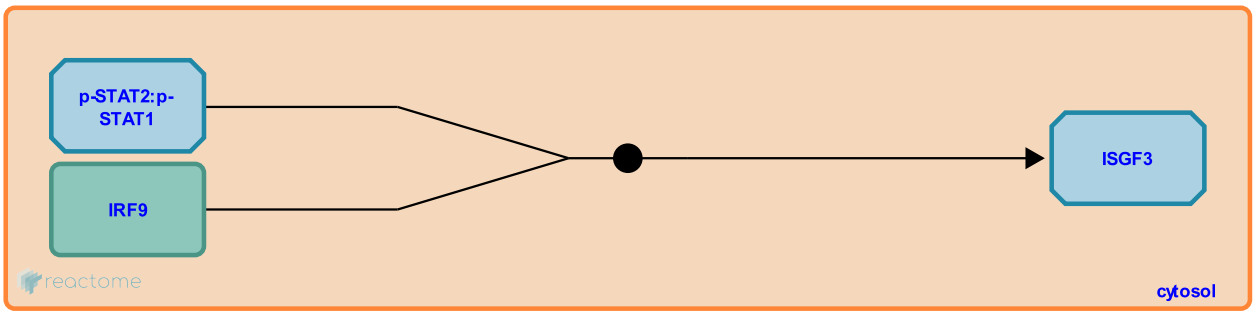
Interaction of IRF9 with p-STAT2:p-STAT1 ↗

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: p-STAT1 dimer binds KPNA1

Literature references

Stark, GR., Darnell JE, Jr., Qureshi, S., Li, X., Leung, S. (1996). Formation of STAT1-STAT2 heterodimers and their role in the activation of IRF-1 gene transcription by interferon-alpha. *J Biol Chem, 271*, 5790-4. ↗

French, DL., Martinez-Moczygemba, M., Reich, NC., Gutch, MJ. (1997). Distinct STAT structure promotes interaction of STAT2 with the p48 subunit of the interferon-alpha-stimulated transcription factor ISGF3. *J Biol Chem, 272*, 20070-6. ↗

Salditt-Georgieff, M., Darnell JE, Jr., Qureshi, SA. (1995). Tyrosine-phosphorylated Stat1 and Stat2 plus a 48-kDa protein all contact DNA in forming interferon-stimulated-gene factor 3. *Proc Natl Acad Sci U S A, 92*, 3829-33. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

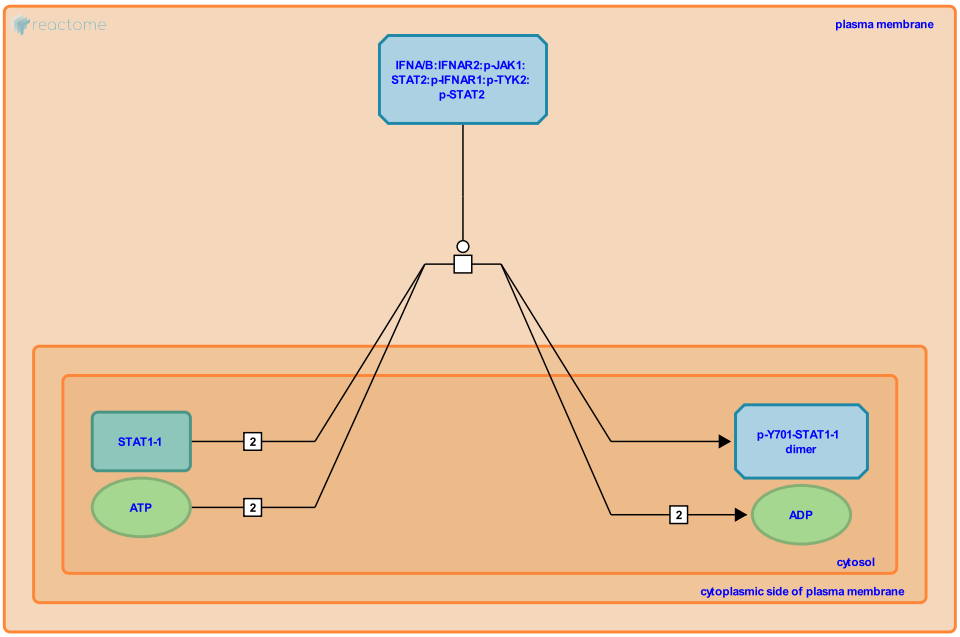
Formation of p-STAT1 homodimer ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909718

Type: transition

Compartments: plasma membrane, cytosol



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: p-STAT1 dimer binds KPNA1

Literature references

Cowburn, D., Horvath, CM., Huang, LH., Darnell JE, Jr., Qureshi, SA., Shuai, K. (1994). Interferon activation of the transcription factor Stat91 involves dimerization through SH2-phosphotyrosyl peptide interactions. *Cell, 76*, 821-8 . ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

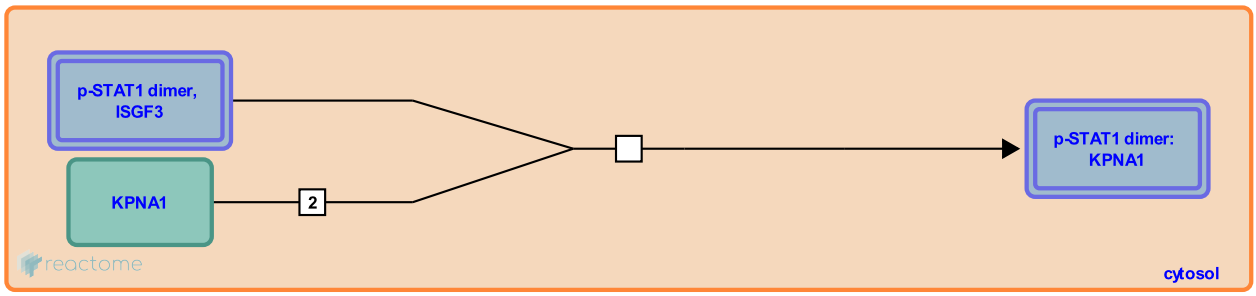
p-STAT1 dimer binds KPNA1 ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-9710959

Type: transition

Compartments: cytosol



Upon viral infection, type I interferons (IFNs), such as IFN-a/b, stimulate the transcription of antiviral interferon-stimulated genes (ISGs) by triggering phosphorylation, dimerization of signal transducer and activator of transcription 1 (STAT1) and STAT2, formation of interferon-stimulated gene factor 3 (ISGF3) complex with interferon regulatory factor 9 (IRF9), and nuclear translocation of ISGF3 complex (Stark GR et al. 2012). STAT1 contains a nonclassical nuclear localization signal (NLS) sequence which is exposed only upon phosphorylation-induced homo- or heterodimerization of STAT1 (Nardozzi J et al. 2010; Fagerlund R et al. 2002; McBride KM et al. 2002). In the cytoplasm, the nonclassical NLS-containing STAT1 dimers are initially recognized by an adaptor molecule, importin subunit α-5 (also known as karyopherin subunit α-1 or KPNA1) (McBride KM et al. 2002; Nardozzi J et al. 2010). KPNA1 then recruits importin β-1 (karyopherin subunit β-1 or KPNB1) via the N-terminal importin β binding (IBB) domain of KPNA1 to form the NLS-cargo:KPNA1:KPNB1 ternary complex (Cingolani G et al. 1999).

Preceded by: Formation of p-STAT1 homodimer, Interaction of IRF9 with p-STAT2:p-STAT1

Followed by: p-STAT1dimer:KPNA1 binds KPNB1

Literature references

Yasuhara, N., Cingolani, G., Nardozzi, J., Wenta, N., Vinkemeier, U. (2010). Molecular basis for the recognition of phosphorylated STAT1 by importin alpha5. *J Mol Biol, 402*, 83-100. ↗

Editions

2021-01-06	Authored	Shamovsky, V.
2021-01-27	Reviewed	D'Eustachio, P.
2021-10-29	Reviewed	Palazzo, AF., Shen, Q.
2021-11-09	Edited	Shamovsky, V.

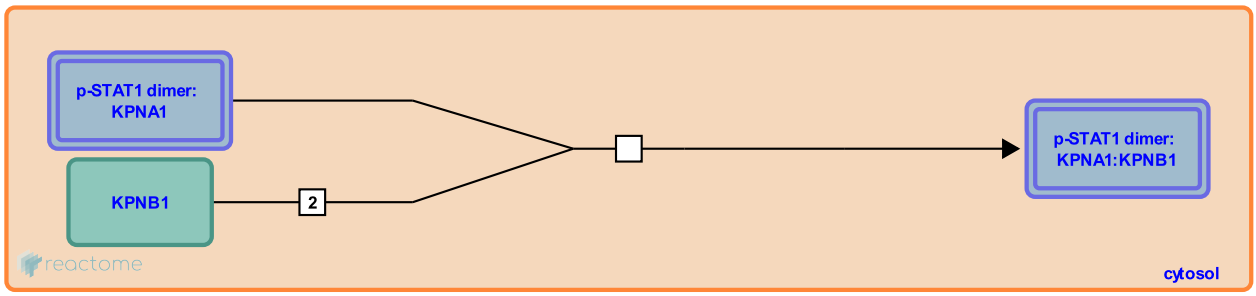
p-STAT1dimer:KPNA1 binds KPNB1 ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-9710963

Type: transition

Compartments: cytosol



Upon viral infection, type I interferons (IFNs) (such as IFN-a/b) stimulate the transcription of antiviral interferon-stimulated genes (ISGs) by triggering phosphorylation, dimerization of signal transducer and activator of transcription 1 (STAT1) and STAT2, formation of interferon-stimulated gene factor 3 (ISGF3) complex with interferon regulatory factor 9 (IRF9), and nuclear translocation of of ISGF3 complex (Stark GR et al. 2012). STAT1 contains a nonclassical nuclear localization signal (NLS) sequence which is exposed only upon phosphorylation-induced homo- or heterodimerization of STAT1 (Nardozzi J et al. 2010; Fagerlund R et al. 2002; McBride KM et al. 2002). In the cytoplasm, the nonclassical NLS of STAT1 dimers is initially recognized by an adaptor molecule, importin subunit α-5 (also known as karyopherin subunit α-1 or KPNA1) (McBride KM et al. 2002; Nardozzi J et al. 2010). KPNA1 then recruits importin β-1 (karyopherin subunit β-1 or KPNB1) via the N-terminal importin β binding (IBB) domain of KPNA1 to form the NLS-cargo:KPNA1:KPNB1 ternary complex (Cingolani G et al. 1999). The formed NLS-cargo:KPNA1:KPNB1 complex is targeted to the nuclear pore complex (NPC) and then passes through nuclear pores via the interaction of KPNB1 with phenylalanine-glycine repeats (FG- repeats) (Moroianu J et al. 1995; McBride KM et al. 2002; Otsuka S et al. 2008; Chook YM & Süel KE. 2011). Many viruses encode proteins that subvert nuclear transport of activated STAT1 to antagonize the IFN signaling pathway (Shen Q et al. 2021). For example, severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) encodes an accessory protein orf6 which is thought to block the nuclear import of STAT1 by binding and tethering KPNA2 and KPNB1 to the endoplasmic reticulum (ER)/Golgi intermediate compartment (ERGIC) thus limiting free KPNB1 in the cytoplasm and reducing the p-STAT1:KPNA1:KPNB1 complex formation (Frieman M et al. 2007). Similar findings were reported for SARS-CoV-2 orf6 which interacts with KPNA2 (Xia H et al. 2020) and blocks the nuclear import of STAT1 (Lei X et al. 2020). In addition, SARS-CoV-2 orf6 also blocks STAT1 nuclear translocation by interacting with the NUP98:RAE1 complex. This disrupts the interaction between NUP98 and the p-STAT1:KPNA1:KPNB1 complex, thus preventing the docking of this complex at the nuclear pore (Miorin L et al. 2020).

Preceded by: p-STAT1 dimer binds KPNA1

Followed by: Translocation of p-STAT1:p-STAT1 dimer to nucleus, Translocation of ISGF3 complex to nucleus

Literature references

Yasuhara, N., Cingolani, G., Nardozzi, J., Wenta, N., Vinkemeier, U. (2010). Molecular basis for the recognition of phosphorylated STAT1 by importin alpha5. *J Mol Biol, 402*, 83-100. ↗

Editions

2021-01-06	Authored	Shamovsky, V.
2021-01-27	Reviewed	D'Eustachio, P.
2021-10-29	Reviewed	Palazzo, AF., Shen, Q.
2021-11-09	Edited	Shamovsky, V.

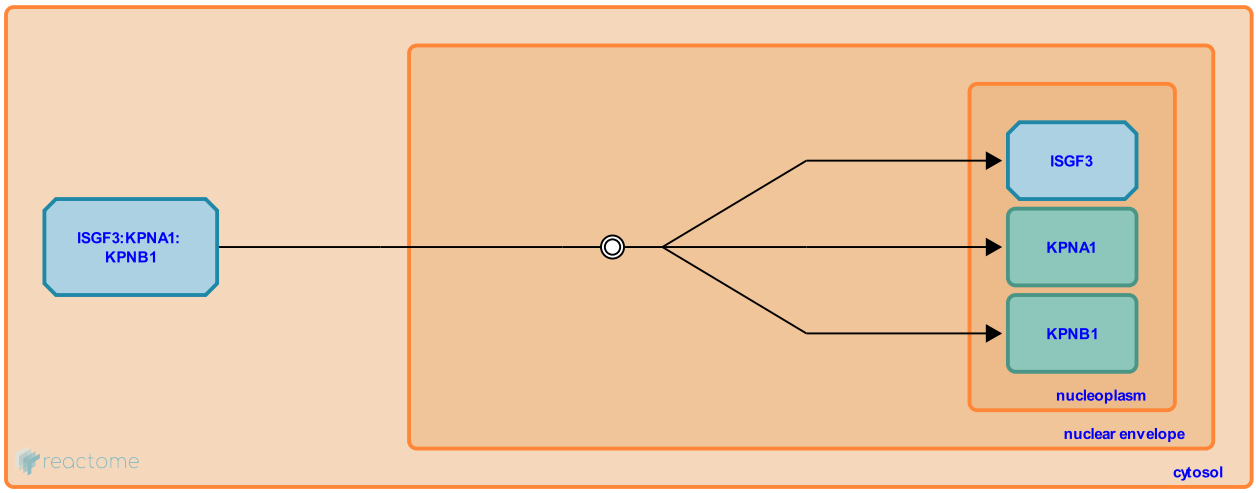
Translocation of ISGF3 complex to nucleus ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909721

Type: dissociation

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: p-STAT1dimer:KPNA1 binds KPNB1

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

Literature references

Szweykowska-Kulinska, Z., Wesoly, J., Bluyssen, HA. (2007). STAT activation and differential complex formation dictate selectivity of interferon responses. *Acta Biochim Pol, 54*, 27-38. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

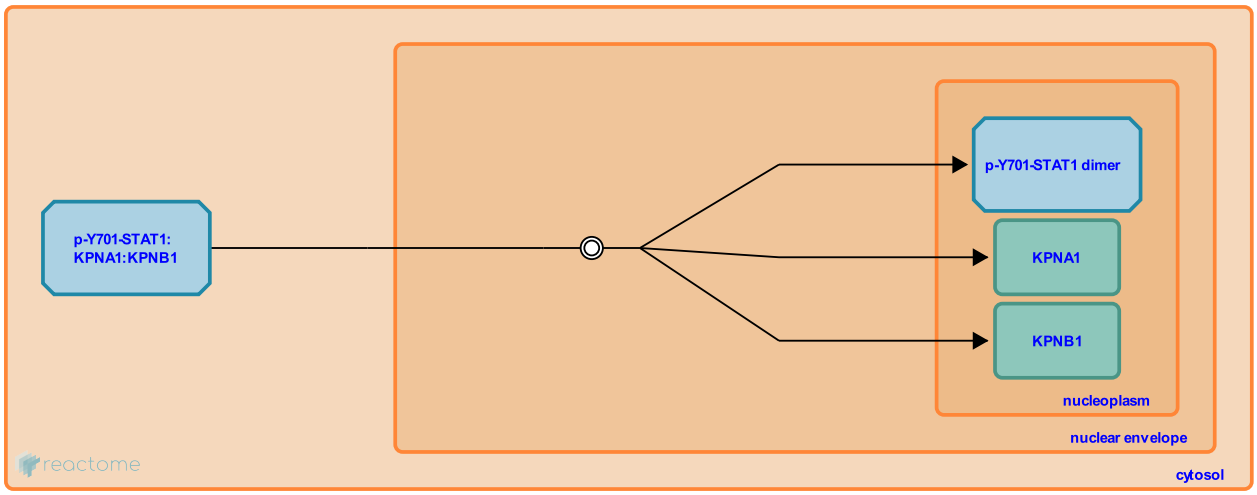
Translocation of p-STAT1:p-STAT1 dimer to nucleus ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-913529

Type: dissociation

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: p-STAT1dimer:KPNA1 binds KPNB1

Literature references

Cowburn, D., Horvath, CM., Huang, LH., Darnell JE, Jr., Qureshi, SA., Shuai, K. (1994). Interferon activation of the transcription factor Stat91 involves dimerization through SH2-phosphotyrosyl peptide interactions. *Cell, 76*, 821-8 . ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

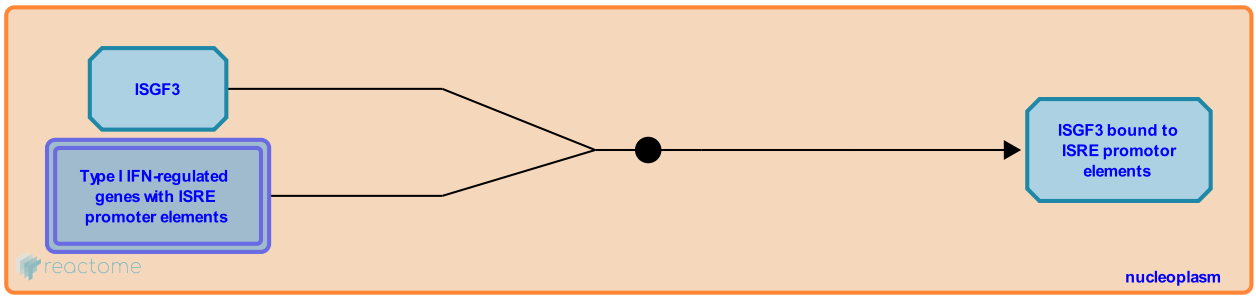
ISGF3 binds the ISRE promoter elements in IFN-stimulated genes ↗

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 induce the transcription of these genes by IFN.

Preceded by: Translocation of ISGF3 complex to nucleus

Followed by: Expression of IFN-induced genes

Literature references

Williams, BR., Sadler, AJ. (2008). Interferon-inducible antiviral effectors. *Nat Rev Immunol, 8*, 559-68. ↗

Liu, YF., Lindner, DJ., Borden, EC., Silverman, RH., Chawla-Sarkar, M., Williams, BR. et al. (2003). Apoptosis and interferons: role of interferon-stimulated genes as mediators of apoptosis. *Apoptosis, 8*, 237-49. ↗

David, M. (1995). Transcription factors in interferon signaling. *Pharmacol Ther, 65*, 149-61. ↗

Silverman, RH., Williams, BR., Der, SD., Zhou, A. (1998). Identification of genes differentially regulated by interferon alpha, beta, or gamma using oligonucleotide arrays. *Proc Natl Acad Sci U S A, 95*, 15623-8. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

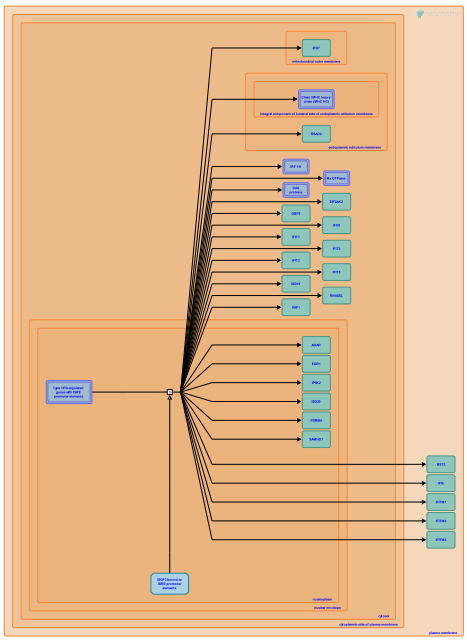
Expression of IFN-induced genes ↗

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

Silverman, RH., Williams, BR., Der, SD., Zhou, A. (1998). Identification of genes differentially regulated by interferon alpha, beta, or gamma using oligonucleotide arrays. *Proc Natl Acad Sci U S A, 95*, 15623-8. ↗

Ozdemir, A., Sun, Y., Leaman, DW., Borden, EC., Yi, T., Chawla-Sarkar, M. et al. (2003). Novel growth and death related interferon-stimulated genes (ISGs) in melanoma: greater potency of IFN-beta compared with IFN-alpha2. *J Interferon Cytokine Res, 23*, 745-56. ↗

McMahon, M., Stark, GR., Kerr, IM., Friedman, RL., Manly, SP. (1984). Transcriptional and posttranscriptional regulation of interferon-induced gene expression in human cells. *Cell, 38*, 745-55. ↗

Tan, YH., Cao, XM., Sukhatme, VP., Guy, GR. (1992). Regulation of the Egr-1 gene by tumor necrosis factor and interferons in primary human fibroblasts. *J Biol Chem, 267*, 1345-9. ↗

Tamai, K., Leaman, DW., Borden, EC., Toji, S., Chawla-Sarkar, M., Reheman, M. et al. (2002). Identification of X-linked inhibitor of apoptosis-associated factor-1 as an interferon-stimulated gene that augments TRAIL Apo2L-induced apoptosis. *J Biol Chem, 277*, 28504-11. ↗

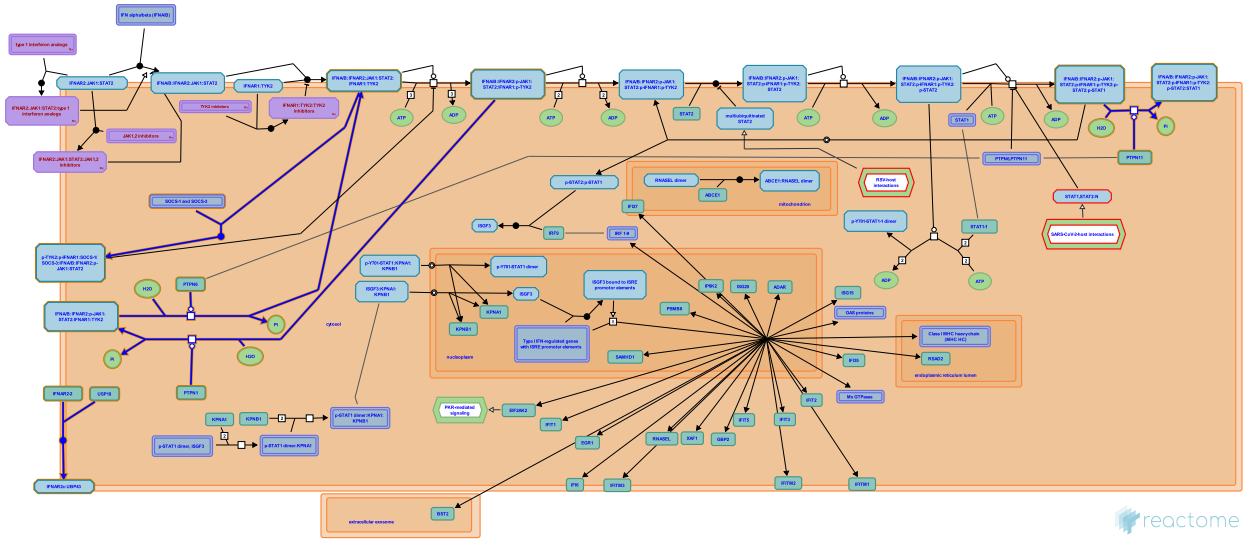
Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

Regulation of IFNA/IFNB signaling ↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-912694



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 controling type I IFN signaling.

Literature references

Hilton, DJ. (1999). Negative regulators of cytokine signal transduction. *Cell Mol Life Sci, 55*, 1568-77. ↗

Fuchs, SY., Malakhova, OA., Zhang, DE., Luo, JK., Kim, KI., Zou, W. et al. (2006). UBP43 is a novel regulator of interferon signaling independent of its ISG15 isopeptidase activity. *EMBO J, 25*, 2358-67. ↗

Alexander, WS., Schreiber, RD., Sheehan, K., Fenner, JE., Starr, R., Metcalf, D. et al. (2006). Suppressor of cytokine signaling 1 regulates the immune response to infection by a unique inhibition of type I interferon activity. *Nat Immunol, 7*, 33-9. ↗

Editions

2010-07-07	Authored, Edited	Garapati, P V.
2010-08-17	Reviewed	Schindler, C., Abdul-Sater, AA.

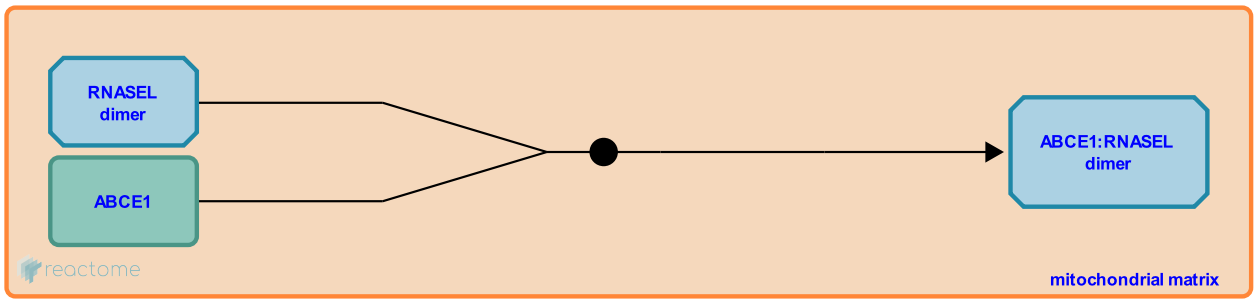
ABCE1 binds RNASEL, inhibiting it ↗

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).

Literature references

Salehzada, T., Martinand, C., Bisbal, C., Lebleu, B., Silhol, M. (1998). RNase L inhibitor (RLI) antisense constructions block partially the down regulation of the 2-5A/RNase L pathway in encephalomyocarditis-virus-(EMCV)-infected cells. *Eur. J. Biochem., 254*, 248-55. ↗

Salehzada, T., Martinand, C., Bisbal, C., Lebleu, B., Le Roy, F., Silhol, M. (2001). The 2-5A/RNase L/RNase L inhibitor (RLI) [correction of (RNI)] pathway regulates mitochondrial mRNAs stability in interferon alpha-treated H9 cells. *J. Biol. Chem., 276*, 48473-82. ↗

Salehzada, T., Martinand, C., Bisbal, C., Lebleu, B., Silhol, M., Montavon, C. (1999). RNase L inhibitor is induced during human immunodeficiency virus type 1 infection and down regulates the 2-5A/RNase L pathway in human T cells. *J. Virol., 73*, 290-6. ↗

Editions

2014-01-06	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

Table of Contents