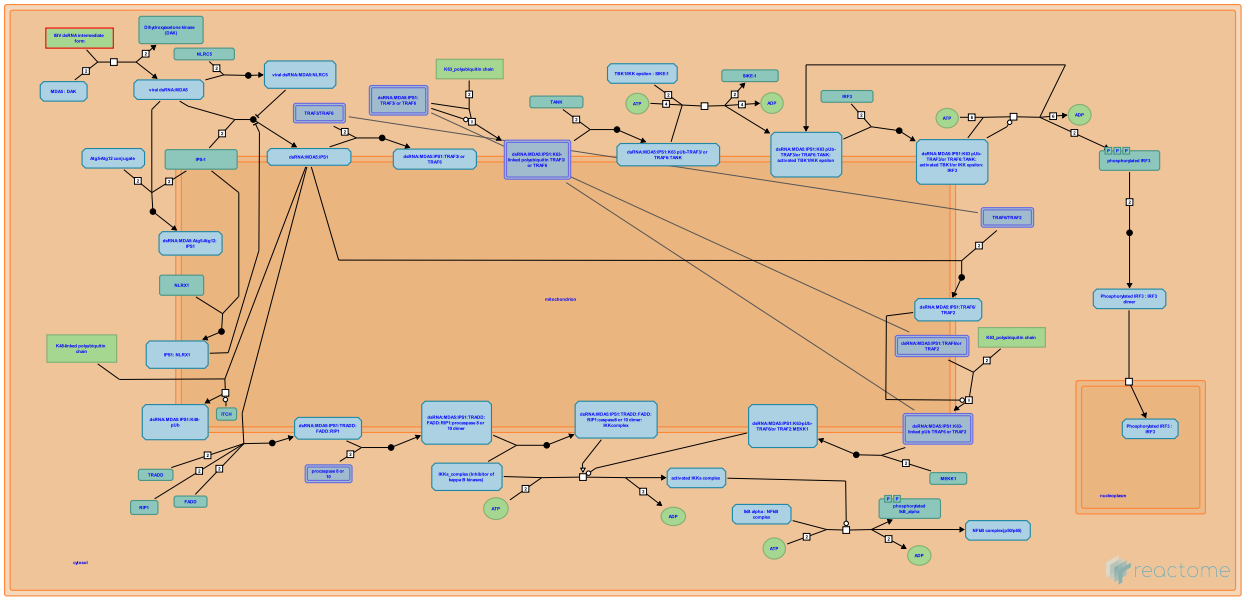
RLR (RIG-like receptor) mediated induction of IFN alpha/beta



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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.

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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).

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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. ↗

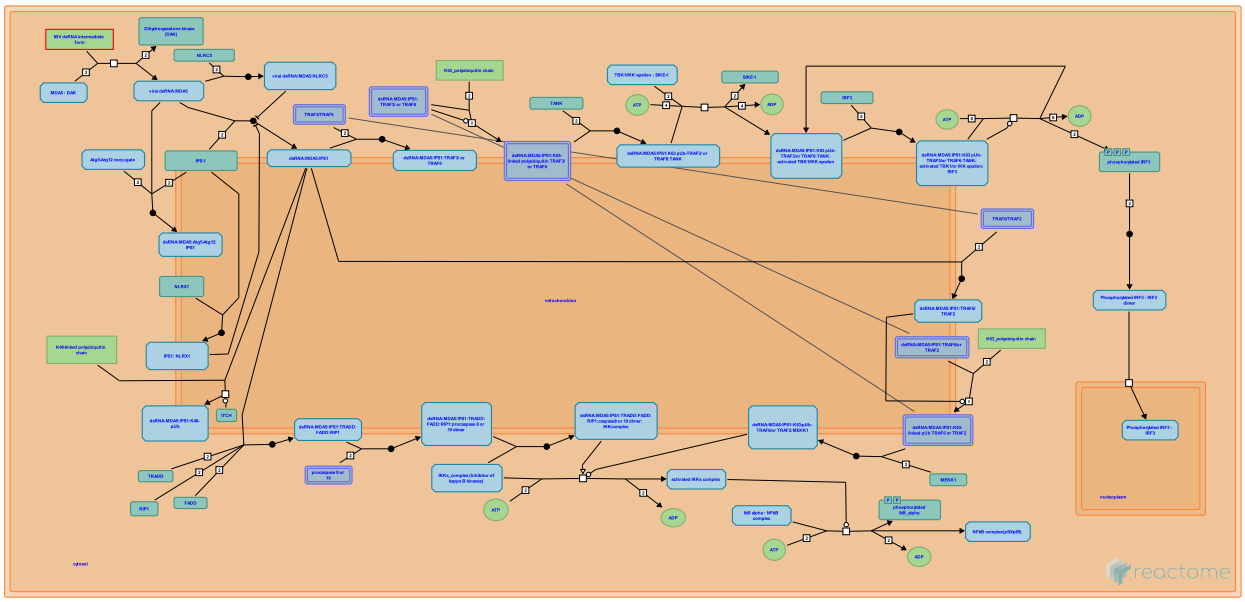
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RLR (RIG-like receptor) mediated induction of IFN alpha/beta ↗

Stable identifier: R-GGA-1227887



In human, RIG-I-like receptor (RLR) family is crucial for triggering response to cytosolic viral RNA. RLR family is composed of retinoic acid-inducible gene 1 protein (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) [Yoneyama et al 2005].

RIG1, MDA5 and LGP2 are cytosolic multidomain proteins. They all contain a central DexD/H-box RNA helicase/adenosine triphosphatase (ATPase) domain that can bind viral RNA, and a C-terminal regulatory domain (RD) that prevents signaling in the absence of viral RNA. RIG-I and MDA5, but not LGP2, also encode two N-terminal caspase activation and recruitment domains (CARDs) that transmit the signal by binding to CARD domain of mitochondrial IFN-beta promoter stimulator protein (IPS-1; also known as MAVS, VISA or Cardif). This CARD-CARD interaction leads to production of IFN alpha/beta and pro inflammatory cytokines. LGP2 that lacks CARD motifs but binds viral RNA is believed to regulate RLR signaling, however the mechanism of the regulation remains unclear; LGP2 was reported to act as negative regulator [Yoneyama et al 2005; Komuro and Horvath 2006; Saito et al 2007], while other studies suggested that LGP2 may cooperate with RIG-1 and MDA5 in sensing certain viral RNA [Venkataraman et al 2007; Satoh et al 2010].

Primary chick embryo cells produced IFN-alpha in response to Newcastle disease virus (NDV) and produced both IFN-alpfa and IFN-beta in response to vaccinia virus or influenza A [Shwartz H et al 2004]. Those viruses have been reported to induce TLR3, RIG-1 and MDA5 signaling in mammals [Delaloye J et al 2009, Kato H et al 2006, Childs et al 2007]. Although RLR signaling is conserved among vertebrates[Sarkar D et al 2008; Zou J et al 2009 and Feng H et al 2011], analysis of chicken genome revealed only orthologs for mammalian MDA5 and LGP2, while RIG-1 gene was not identified [Sarkar D et al 2008; Zou J et al 2009; and Barber MR et al 2010].

Literature references

Webster, RG., Barber, MR., Magor, KE., Aldridge JR, Jr. (2010). Association of RIG-I with innate immunity of ducks to influenza. *Proc Natl Acad Sci U S A, 107*, 5913-8. ↗

Fisher, PB., Desalle, R., Sarkar, D. (2008). Evolution of MDA-5/RIG-I-dependent innate immunity: independent evolution by domain grafting. *Proc Natl Acad Sci U S A, 105*, 17040-5. ↗

Kikuchi, M., Loo, YM., Fujita, T., Matsumoto, K., Imaizumi, T., Taira, K. et al. (2005). Shared and unique functions of the DExD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. *J Immunol, 175*, 2851-8. ↗

Editions

2011-01-05	Authored	Shamovsky, V.
2011-05-11	Edited	Shamovsky, V.
2011-05-16	Reviewed	Garapati, P V.

dsRNA binds to MDA5 ↗

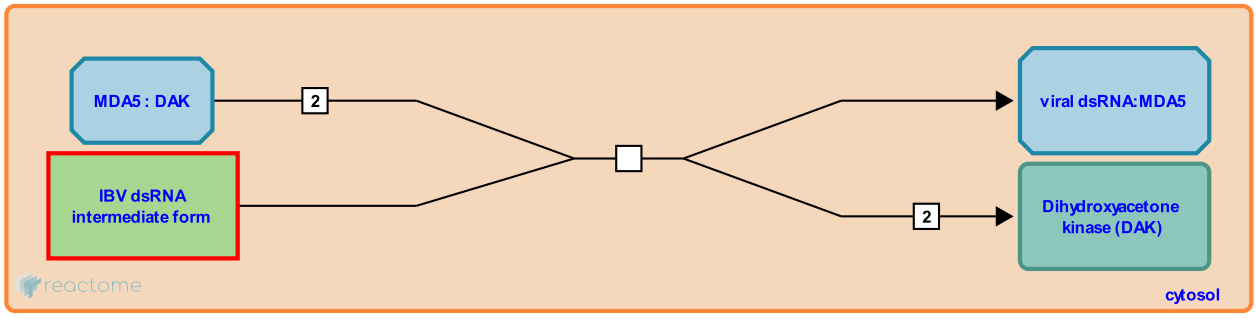
Location: RLR (RIG-like receptor) mediated induction of IFN alpha/beta

Stable identifier: R-GGA-1227694

Type: transition

Compartments: cytosol

Inferred from: viral dsRNA binds IFIH1:TKFC (Homo sapiens)



Poly(I)-poly(C) was reported to trigger MDA5 mediated IFN signaling in mammals (Kato H et al., 2006; Gitlin L et al., 2006). Poly(I)-poly(C)-induced IFN production was inhibited in the presence of paramyxovirus V proteins both in human and in chicken cells. In addition, paramyxovirus V proteins were demonstrated to target helicase domain of MDA5, but not RIG-1 (Childs et al., 2007, Childs et al., 2009). Furthermore, overexpression of chicken MDA5 has been shown to induce IFN promoter in chicken fibroblast cell line DF1, but not in human Vero cells. Similar to chicken MDA5, human MDA5 was unable to function in avian cells. Therefore, authors suggested that chicken MDA5 may function similar to its mammalian counterpart, but in a species-specific manner [Childs et al., 2007].

Chicken MDA5 shares 60% overall sequence identity with human MDA5. Detailed analysis of human and chicken MDA5 revealed considerable sequence divergence between N-terminal effector CARD domains (43% amino acid identity), while the C-terminal helicase domains showed a relatively high degree of conservation (67% amino acid identity with extended regions of over 80%) (Childs et al., 2007).

Followed by: Activated MDA5 binds IPS-1

Literature references

Webster, RG., Barber, MR., Magor, KE., Aldridge JR, Jr. (2010). Association of RIG-I with innate immunity of ducks to influenza. *Proc Natl Acad Sci U S A, 107*, 5913-8. ↗

Forlenza, M., Maier, HJ., Langereis, MA., Koumans, J., Fernandez-Gutierrez, M., Wiegertjes, GF. et al. (2015). Activation of the chicken type I interferon response by infectious bronchitis coronavirus. *J. Virol., 89*, 1156-67. ↗

Goodbourn, S., Ross, C., Stock, N., Randall, RE., Childs, KS., Skinner, M. et al. (2007). mda-5, but not RIG-I, is a common target for paramyxovirus V proteins. *Virology, 359*, 190-200. ↗

Zhang, Y., Li, S., Tien, P., Chen, D., Xu, LG., Zhang, M. et al. (2007). Negative regulation of MDA5- but not RIG-I-mediated innate antiviral signaling by the dihydroxyacetone kinase. *Proc Natl Acad Sci U S A, 104*, 11706-11. ↗

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Activated MDA5 binds IPS-1 ↗

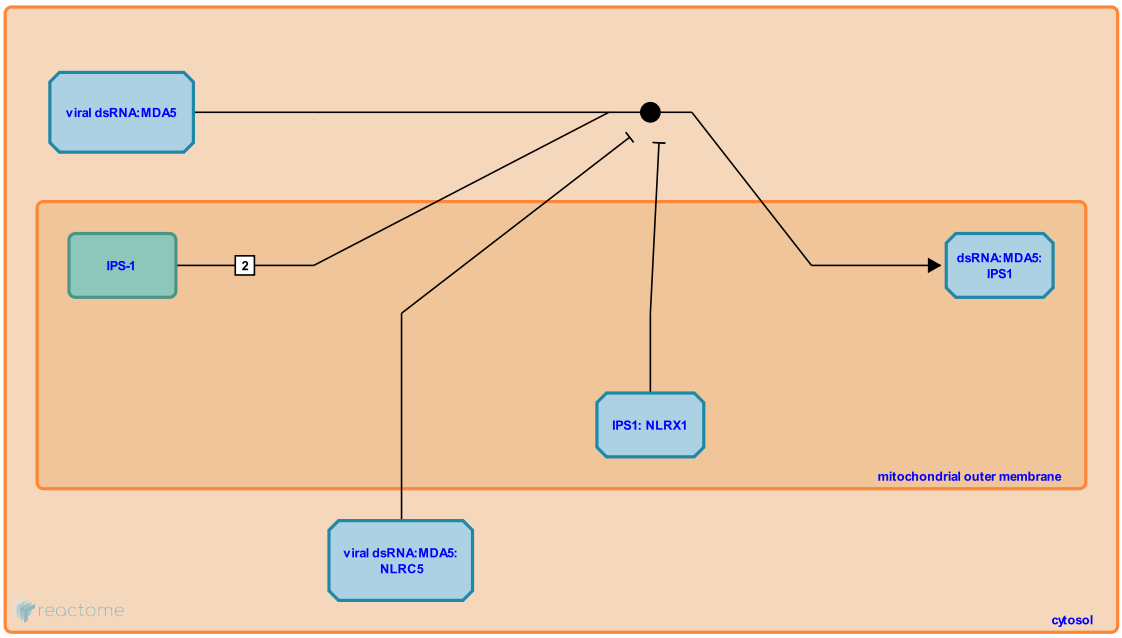
Location: RLR (RIG-like receptor) mediated induction of IFN alpha/beta

Stable identifier: R-GGA-1227709

Type: binding

Compartments: cytosol, mitochondrial outer membrane

Inferred from: viral dsRNA:IFIH1, viral dsRNA:K63polyUb-DDX58 bind MAVS (Homo sapiens)



Predicted chicken interferon beta promoter stimulator 1(IPS1) protein shows 27 and 31% amino acid sequence identity to its human and mouse orthologs respectively. Here we assume that chicken IPS1 behaves similar to its human counterpart upon viral stimulation.

In mammals, viral RNA binding to RLRs is believed to induce conformational changes, which unmask CARD regions of RIG-1 and MDA5. The CARDs of RLR interact with N- terminal CARD domain of mitochondria-bound adaptor protein - IPS-1, also known as VISA, MAVS or CARDIF [Yoneyama et al 2005, Saito et al 2007, Kawai et al 2005, Potter et al 2008].

Preceded by: dsRNA binds to MDA5

Literature references

Xu, LG., Shu, HB., Han, KJ., Wang, YY., Zhai, Z., Li, LY. (2005). VISA is an adapter protein required for virus-triggered IFN-beta signaling. *Mol Cell, 19*, 727-40. ↗

Taylor, GL., Potter, JA., Randall, RE. (2008). Crystal structure of human IPS-1/MAVS/VISA/Cardif caspase activation recruitment domain. *BMC Struct Biol, 8*, 11. ↗

Takeuchi, O., Ishii, KJ., Kumar, H., Sato, S., Kawai, T., Takahashi, K. et al. (2005). IPS-1, an adaptor triggering RIG-I- and Mda5-mediated type I interferon induction. *Nat Immunol, 6*, 981-8. ↗

Editions

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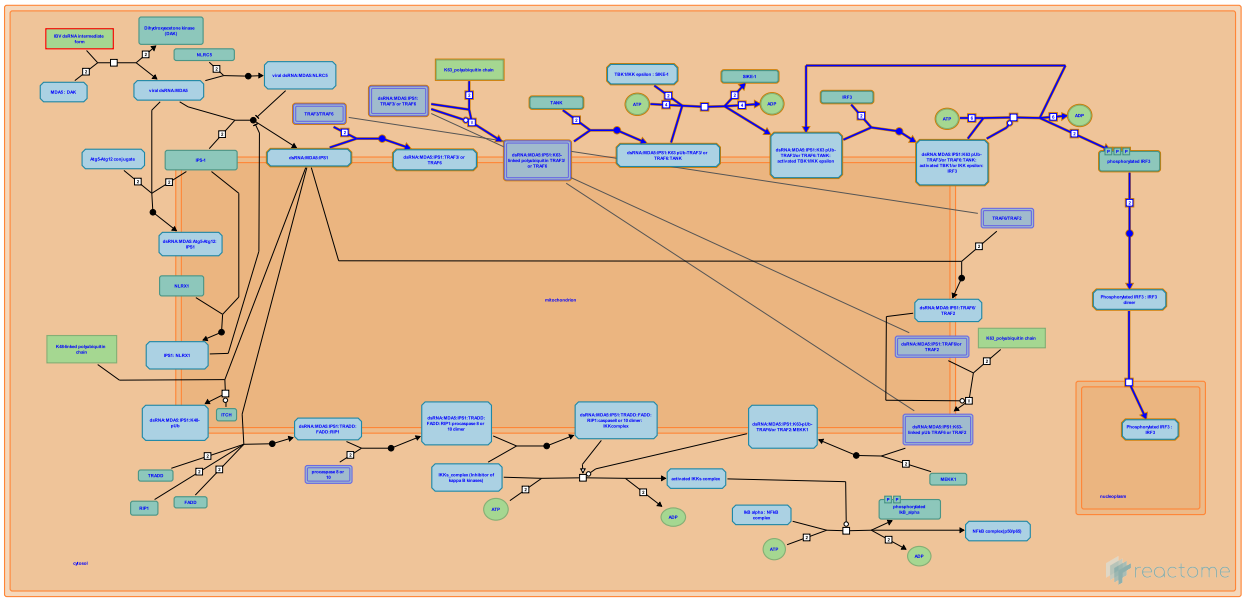
TRAF mediated activation of IRF ↗

Location: RLR (RIG-like receptor) mediated induction of IFN alpha/beta

Stable identifier: R-GGA-1227882

Inferred from: TRAF3-dependent IRF activation pathway (Homo sapiens), TRAF6 mediated IRF7 activation (Homo sapiens)



Once activated, IPS-1 recruits TRAFs (TNF receptor associated factor protein family members) to the RIG-1/MDA5 receptor complex. TRAF3 and TRAF6 act as a scaffold for the assembly of the signaling complex composed of TBK1/ IKK epsilon, leading to the activation of transcription factors IRF3 and IRF7. TRAF6-induced activation of IRF is likely to be specific for IRF7, while TRAF3 is thought to activate both IRF3 and IRF7 [Konno H et al 2009, Oganesyan G et al 2006].

Transient transfection experiments in human embryonic kidney (HEK) 293 cells revealed that TRAF6 associates with IPS-1, TBK1, IKKi and TANK [Konno H et al 2009]. TRAF3 was also shown to form complexes with IPS-1, TBK1 and IKKi [Oganesyan G et al 2006, Alff PJ et al 2008, Saha SK et al 2006]

Literature references

Takeuchi, O., Kato, A., Goto, H., Tsunetsugu-Yokota, Y., Su, B., Yamazaki, K. et al. (2009). TRAF6 establishes innate immune responses by activating NF-kappaB and IRF7 upon sensing cytosolic viral RNA and DNA. *PLoS One, 4*, e5674. ↗

Perry, A., Saha, SK., Oganesyan, G., He, JQ., Guo, B., Shahangian, A. et al. (2006). Critical role of TRAF3 in the Toll-like receptor-dependent and -independent antiviral response. *Nature, 439*, 208-11. ↗

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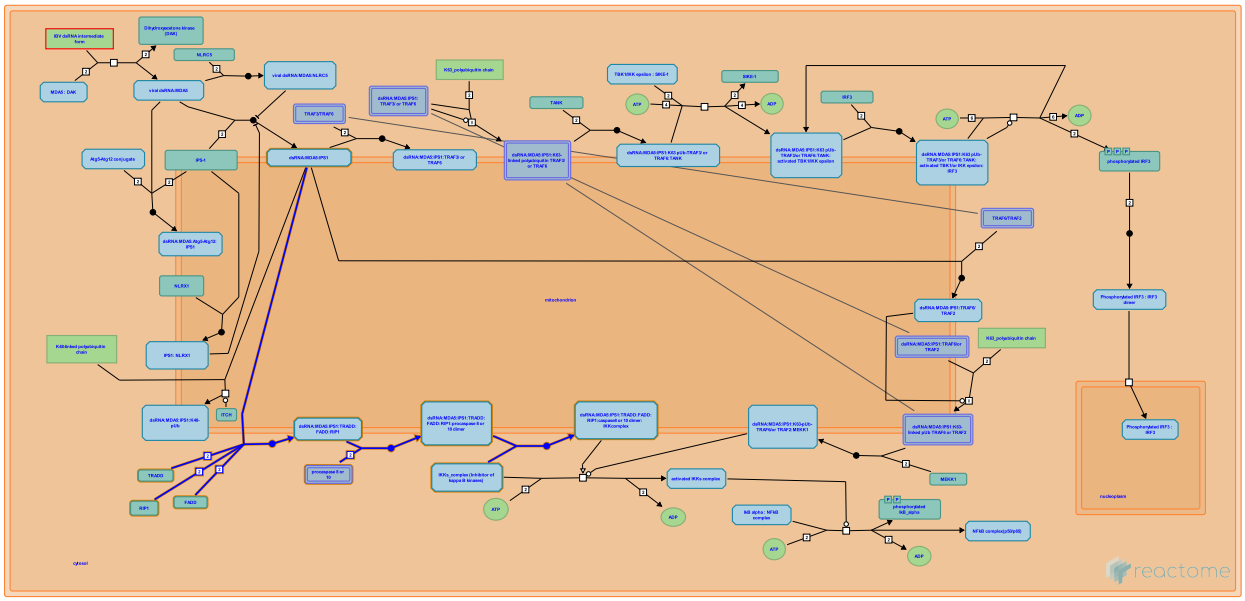
Caspase-8 and -10 mediated induction of NF-kB ↗

Location: RLR (RIG-like receptor) mediated induction of IFN alpha/beta

Stable identifier: R-GGA-1227739

Inferred from: NF-kB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10 (Homo sapiens)



In mammals, virus-triggered RIG-1 or MDA5 receptor complex has been shown to recruit initiator caspases-8 and -10 via adapter FADD (Fas-associated death domain-containing protein) leading to NF-kB activation [Takahashi K et al 2006]. Other FADD and caspase-interacting adaptors - RIP-1(receptor interacting protein-1) and TRADD (TNFR-associated death domain) - have been also implicated in RLR-dependent antiviral responses [Kawai T et al 2005, Balachandran M et al 2004, Michallet MC et al 2008]. FADD, TRADD and RIP-1 form signaling complexes that coordinate both apoptotic and non-apoptotic functions of caspases.

It has been suggested that large prodomains with DED (death effector domains) of caspases-8/10 can function as a bridge to link downstream mediators like IKK complex to the adaptor proteins [Chaudhary PM et al 2000, Lamkanfi M et al 2006]. Recruitment of caspases-8/10 to activated receptor complex is also believed to result in conformational changes leading to caspase auto-proteolysis. Processed caspases were shown to activate NF-kB signaling. However, the detailed mechanism of caspase-mediated NF-kB induction remains unclear [Takahashi K et al 2006, Lamkanfi M et al 2006].

Literature references

Kawai, T., Sato, S., Kumar, H., Akira, S., Yonehara, S., Takahashi, K. (2006). Roles of caspase-8 and caspase-10 in innate immune responses to double-stranded RNA. *J Immunol, 176*, 4520-4. ↗

Vandenabeele, P., Vanden Berghe, T., Lamkanfi, M., Declercq, W. (2006). Caspases leave the beaten track: caspase-mediated activation of NF-kappaB. *J Cell Biol, 173*, 165-71. ↗

Miyashita, T., Shikama, Y., Yamada, M. (2003). Caspase-8 and caspase-10 activate NF-kappaB through RIP, NIK and IKKalpha kinases. *Eur J Immunol, 33*, 1998-2006. ↗

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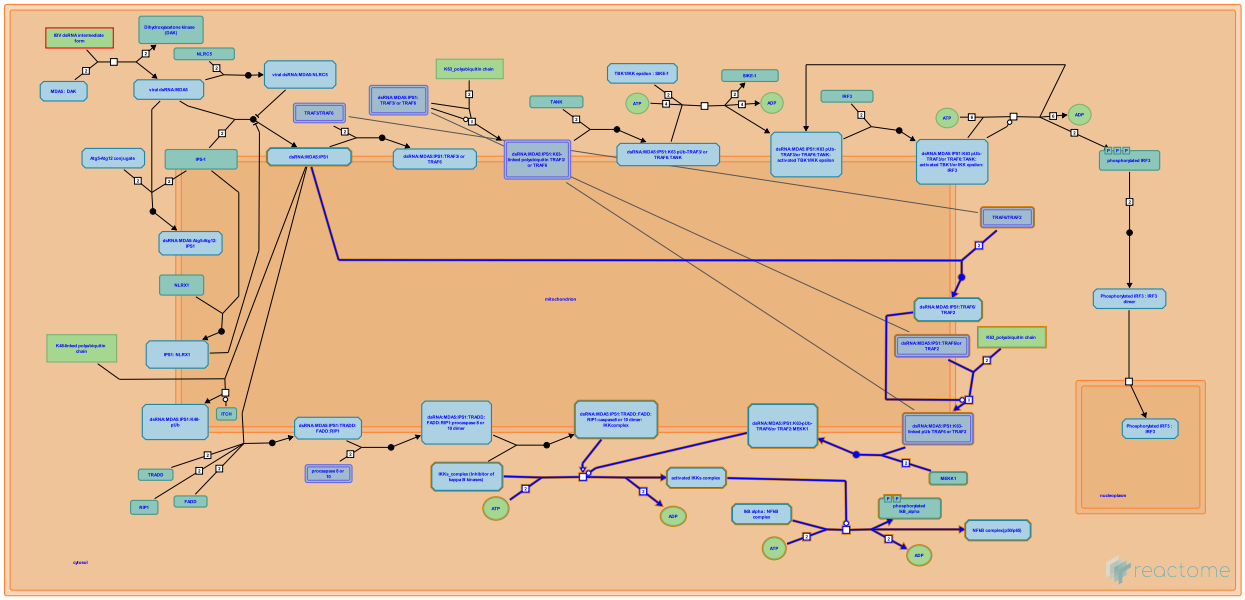
TRAF6 mediated NF-kB activation ↗

Location: RLR (RIG-like receptor) mediated induction of IFN alpha/beta

Stable identifier: R-GGA-1227892



Although RLR-mediated signaling to NFkB and MAPK shares similarity with better-characterized TLR and TNF signaling pathways, many of the details need to be clarified. Thus, TGF-beta activated kinase 1(TAK1, also known as MAP3K7) - an essential mediator in TLR signaling downstream of TRAF6, was shown to associate with IPS-1 [Xu LG et al 2005]. However, there are conflicting reports on the role of TAK1 in RIG-1/IPS-1 mediated NFkB activation [Konno H et al 2009, Yoshida R et al 2008, Mikkelsen SS et al 2009].

Another MAP3K, MEKK1, has been reported to induce IKK and MAPK activation in RIG1 signaling pathway in response to dsRNA.[Yoshida R et al 2008].

TNF receptor associated factor (TRAF) protein family members are E3 ligases that have been implicated in various signal transduction pathways including RLR signaling and Toll-like receptors (TLRs) leading to activation of NFkB, MAPK and IRF family members [Oganesyan G et al 2006, Xia et al 2009, Sasai M et al 2010].

Literature references

Xu, LG., Shu, HB., Han, KJ., Wang, YY., Zhai, Z., Li, LY. (2005). VISA is an adapter protein required for virus-triggered IFN-beta signaling. *Mol Cell, 19*, 727-40. ↗

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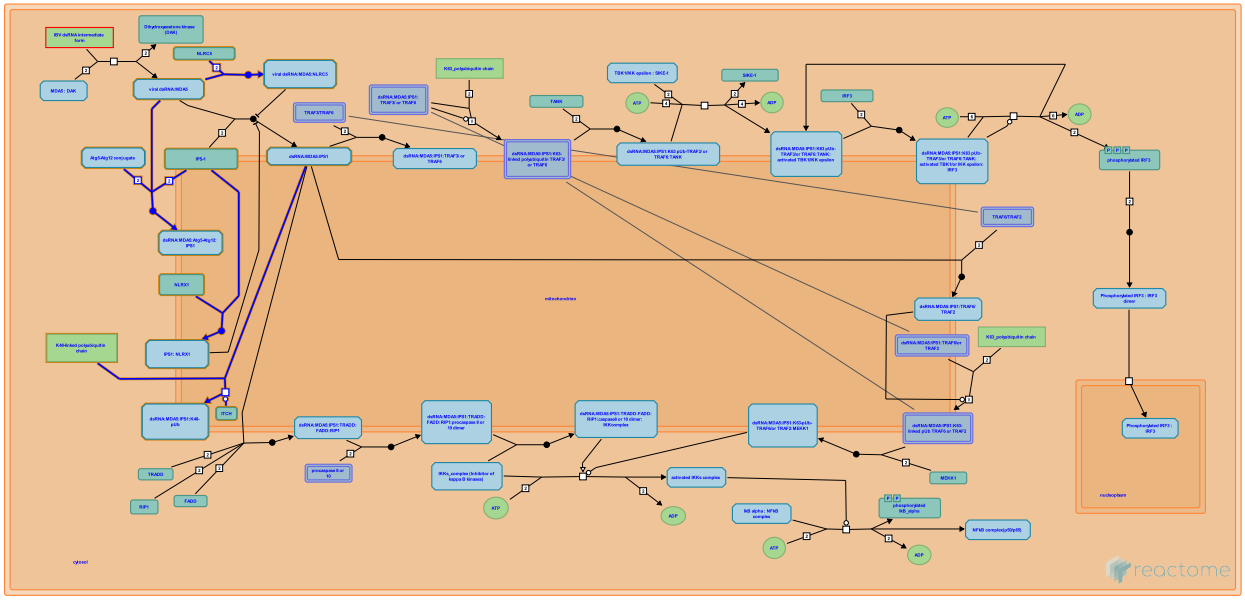
Negative Regulation of MDA5 signaling ↗

Location: RLR (RIG-like receptor) mediated induction of IFN alpha/beta

Stable identifier: R-GGA-1227888

Inferred from: Negative regulators of DDX58/IFIH1 signaling (Homo sapiens)



Antiviral responses must be tightly regulated in order to prevent uncontrolled production of type I IFN that may lead to damage of host's cells and tissues.

Literature references

Horvath, CM., Komuro, A., Bamming, D. (2008). Negative regulation of cytoplasmic RNA-mediated antiviral signaling. *Cytokine, 43*, 350-8. ↗

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