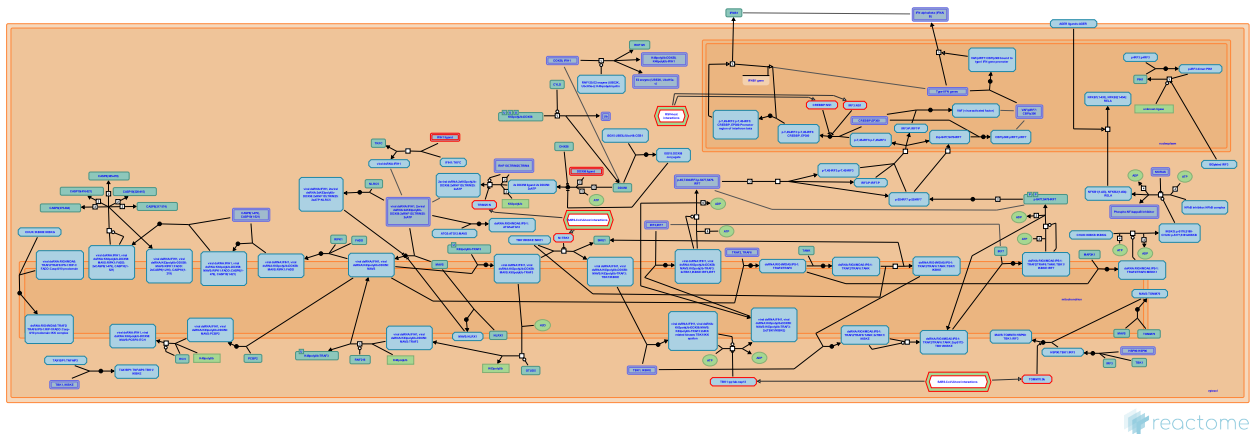


DDX58/IFIH1-mediated induction of interferon-alpha/beta



Akira, S., D'Eustachio, P., Garapati, P V., Kawai, T., Messina, F., Ramos, CH., Shamovsky, V.

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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](https://reactome.org/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.

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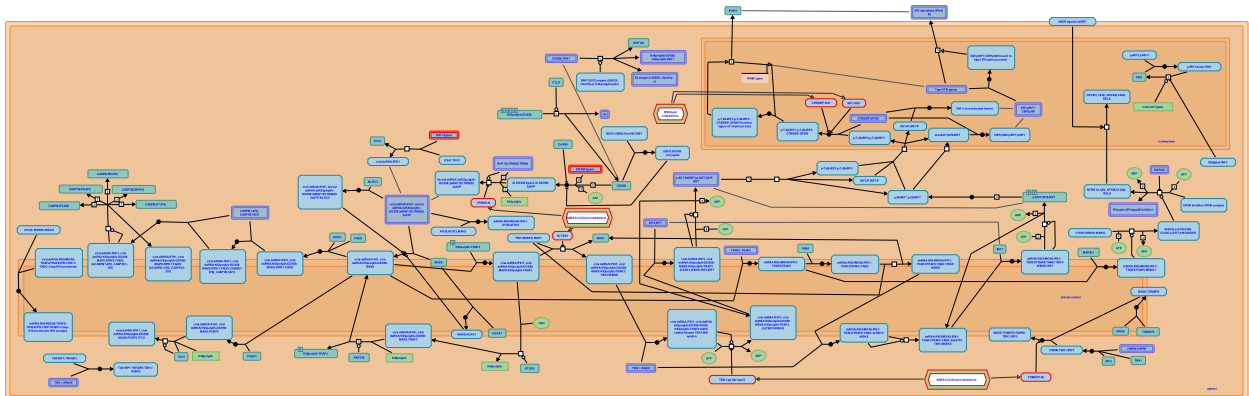
Reactome database release: 88

This document contains 6 pathways and 7 reactions ([see Table of Contents](#))

DDX58/IFIH1-mediated induction of interferon-alpha/beta ↗

Stable identifier: R-HSA-168928

Compartments: mitochondrial outer membrane



reactome

RIG-I-like helicases (RLHs) the retinoic acid inducible gene-I (RIG-I) and melanoma differentiation associated gene 5 (MDA5) are RNA helicases that recognize viral double-stranded RNA (dsRNA) present within the cytoplasm (Yoneyama M & Fujita T 2007, 2008). Upon viral infection dsRNA is generated by positive-strand RNA virus families such as Flaviviridae and Coronaviridae, negative-strand RNA virus families including Orthomyxoviridae and Paramyxoviridae, and DNA virus families such as Herpesviridae and Adenoviridae (Weber F et al. 2006; Son KN et al. 2015). Functionally RIG-I and MDA5 positively regulate the IFN genes in a similar fashion, however they differ in their response to different viral species. RIG-I is essential for detecting influenza virus, Sendai virus, VSV and Japanese encephalitis virus (JEV), whereas MDA5 is essential in sensing encephalomyocarditis virus (EMCV), Mengo virus and Theiler's virus, all of which belong to the picornavirus family. RIG-I and MDA5 signalling results in the activation of IKK epsilon and (TAK1 binding kinase 1) TBK1, two serine/threonine kinases that phosphorylate interferon regulatory factor 3 and 7 (IRF3 and IRF7). Upon phosphorylation, IRF3 and IRF7 translocate to the nucleus and subsequently induce interferon alpha (IFNA) and interferon beta (IFNB) gene transcription (Yoneyama M et al. 2004; Yoneyama M & Fujita T 2007, 2008).

Literature references

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2010-08-02	Authored, Edited	Garapati, P V.
2010-10-30	Reviewed	Akira, S., Kawai, T.

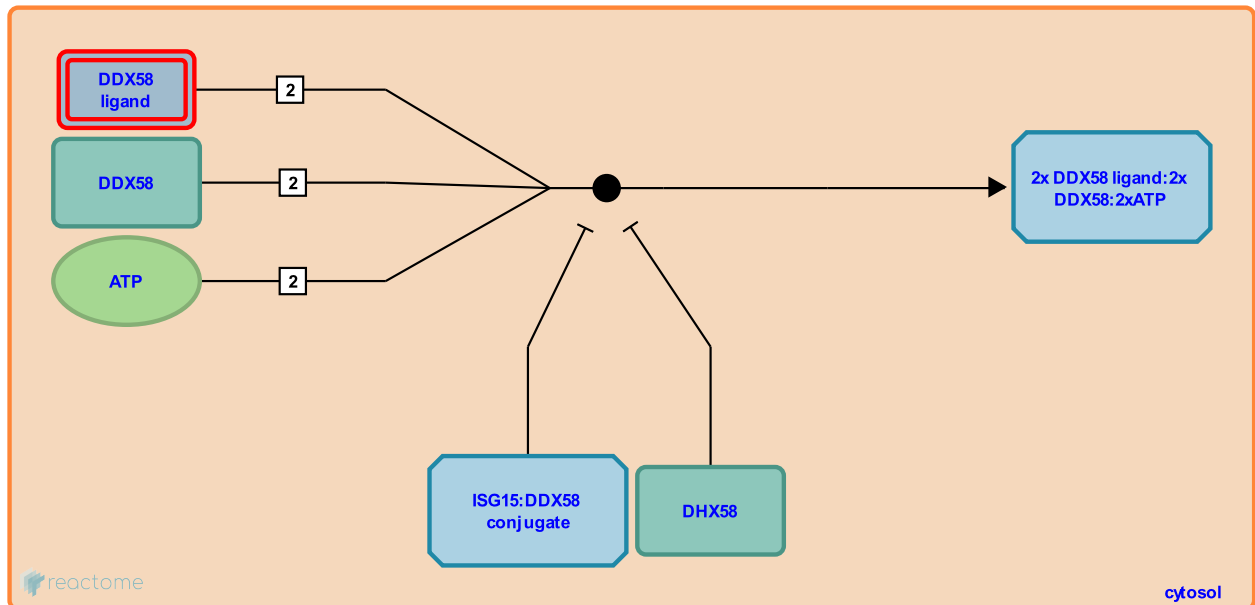
viral dsRNA binds DDX58 ↗

Location: DDX58/IFIH1-mediated induction of interferon-alpha/beta

Stable identifier: R-HSA-168935

Type: binding

Compartments: cytosol



LGP2 acts as a natural negative regulator of dsRNA signaling. Several mechanisms may account for the LGP2 inhibitory effects. As a homolog of RIG-I, one attractive model is that LGP2 can sequester RNA ligands from recognition by RIG-I/MDA5. LGP2 has also been demonstrated to associate with RIG-I to inhibit its auto-oligomerization via the LGP2 C-terminal region comparable to the RIG-I repressor domain. In this model, dimerization of RIG-I by viral RNA, proposed to be an active form of RIG-I, is replaced by a RIG-I:LGP2 hetero-oligomer.

Probable ATP-dependent RNA helicase DDX58 (DDX58, RIG-I, RIG-1) has two caspase recruitment domains (CARD) in its N-terminus, a DExD/H helicase domain with an ATP binding motif in the middle and a repressor domain (RD) in the C-terminus. In the absence of appropriate stimulation, DDX58 is in a 'closed' conformation in which the repressor domain physically interacts with the helicase domain masking CARD. Upon viral infection, the free triphosphate structure at the 5' end of viral RNAs activates DDX58 by binding to its RNA helicase domain. This provokes a change in DDX58 conformation exposing the CARD leading to DDX58 dimerization, allowing it to interact with Mitochondrial antiviral-signaling protein (MAVS, IPS-1).

ISG15 is an ubiquitin (Ub)-like protein which is conjugated to intracellular proteins via an isopeptide bond. Similar to ubiquitination, the conjugation of ISG15 (ISGylation) requires a three-step process, involving an E1 activating enzyme (UBE1L), an E2 conjugating enzyme (UbcM8/H8), and HERC5/Ceb1 an IFN-inducible ISG15-specific E3 ligase. ISG15 conjugation may play an important regulatory role in IFN-mediated antiviral responses. IFN induces ISG15 conjugation to DDX58 negatively regulating DDX58-mediated antiviral signaling. ISGylated DDX58 becomes subject to an irreversible biochemical process, such as proteolysis or proteasomal degradation.

Followed by: DDX58 is K63 polyubiquitinated

Literature references

Taira, K., Shinobu, N., Yoneyama, M., Fujita, T., Miyagishi, M., Kikuchi, M. et al. (2004). The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat Immunol*, 5, 730-7. ↗

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Editions

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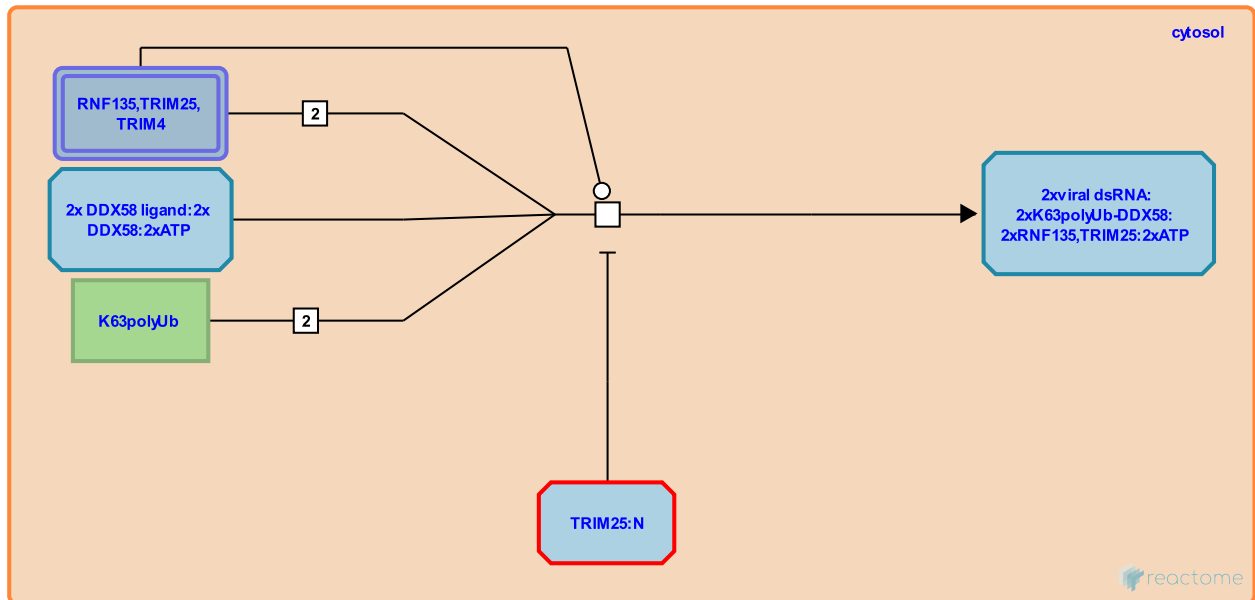
DDX58 is K63 polyubiquitinated ↗

Location: [DDX58/IFIH1-mediated induction of interferon-alpha/beta](#)

Stable identifier: R-HSA-918224

Type: transition

Compartments: cytosol



On viral infection antiviral innate immune response receptor RIG-I (RIG-I, also known as probable ATP-dependent RNA helicase DDX58 or DEAD box protein 58) undergoes robust ubiquitination at its N-terminal Caspase activation and recruitment domain (CARD) region. E3 ubiquitin/ISG15 ligase TRIM25 (TRIM25), TRIM4, members of the tripartite motif (TRIM) protein family, and E3 ubiquitin-protein ligase RNF135 (RNF135, REUL) are the E3 ligases involved in K63-linked polyubiquitination (K63polyUb) of DDX58 (Gack MU 2007; Gao D et al. 2009; Oshiumi H et al. 2009; Yan J et al. 2014). TRIM25 contains a cluster of domains including a RING-finger domain, a B box/coiled-coil domain and a SPRY domain. The interaction is mediated by the SPRY domain of TRIM25 and the N-terminal CARDs of DDX58. The polyubiquitin chains added by TRIM25 are unanchored. The lysine-172 (K172) residue of DDX58 is critical for efficient TRIM25-mediated ubiquitination and for binding of Mitochondrial Antiviral-Signaling protein (MAVS, IPS-1), as well as the ability of DDX58 to induce antiviral signal transduction (Gack MU 2007). RNF135 associates with DDX58 through its PRY and SPRY domains. The K154, K164, and K172 residues of the DDX58 CARD domain are critical for efficient RNF135-mediated ubiquitination and for the ability of DDX58 to induce antiviral signal transduction. (Gao D et al. 2009). TRIM4 also interacts with the N-terminal CARDs of DDX58 and targets DDX58 at K154, K164, and K172 for K63-linked polyubiquitination (Yan J et al. 2014).

The severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) nucleocapsid (N) protein was found to inhibit TRIM25-mediated DDX58 ubiquitination upon coexpression in HEK293T cells in a dose-dependent manner (Hu Y et al. 2017). Similar results were reported for the SARS-CoV-2 N protein (Gori Savellini G et al. 2021).

Preceded by: [viral dsRNA binds DDX58](#)

Followed by: [viral dsRNA:IFIH1](#), [viral dsRNA:K63polyUb-DDX58 bind MAVS](#)

Literature references

Takeuchi, O., Gack, MU., Joo, CH., Inoue, S., Akira, S., Shin, YC. et al. (2007). TRIM25 RING-finger E3 ubiquitin ligase is essential for RIG-I-mediated antiviral activity. *Nature*, 446, 916-920. ↗

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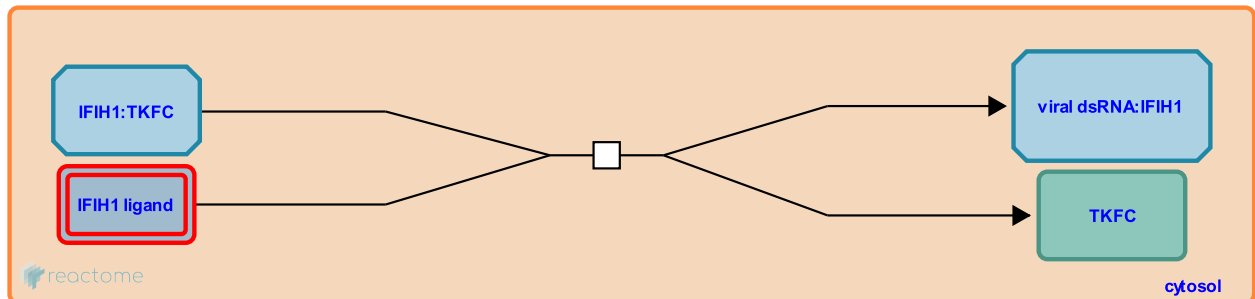
viral dsRNA binds IFIH1:TKFC ↗

Location: DDX58/IFIH1-mediated induction of interferon-alpha/beta

Stable identifier: R-HSA-913725

Type: transition

Compartments: cytosol



Interferon-induced helicase C domain-containing protein 1 (IFIH1, MDA5) is the closest relative of Probable ATP-dependent RNA helicase DDX58 (DDX58, RIG-I). It contains two Caspase activation and recruitment domain (CARD)-like regions, a DExD/H helicase domain, and a C-terminal region similar to the RD of DDX58. IFIH1, via its C-terminal domain (CTD), preferentially binds dsRNA with blunt ends. It does not associate with dsRNA having 5' or 3' overhangs. Upon binding dsRNA, IFIH1 is presumed to undergo a structural alteration that unmasks the CARDs enabling them to recruit downstream signal transducer proteins. Dihydroxyacetone kinase (DAK, TKFC) binds to the CARD domains of IFIH1, acting as a negative regulator. It is released upon the conformational change induced by viral RNA binding, allowing the CARD domains to bind to the CARD of Mitochondrial antiviral-signaling protein (MAVS, IPS-1).

Followed by: [viral dsRNA:IFIH1](#), [viral dsRNA:K63polyUb-DDX58 bind MAVS](#)

Literature references

Strong, RK., Xu, H., Lu, C., Li, X., Stewart, M., Li, P. et al. (2009). Structural basis of double-stranded RNA recognition by the RIG-I like receptor MDA5. *Arch Biochem Biophys*, 488, 23-33. ↗

Hiiragi, A., Kawai, T., Mikamo-Satoh, E., Takeuchi, O., Fujita, T., Matsushita, K. et al. (2008). Length-dependent recognition of double-stranded ribonucleic acids by retinoic acid-inducible gene-I and melanoma differentiation-associated gene 5. *J Exp Med*, 205, 1601-10. ↗

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. ↗

Editions

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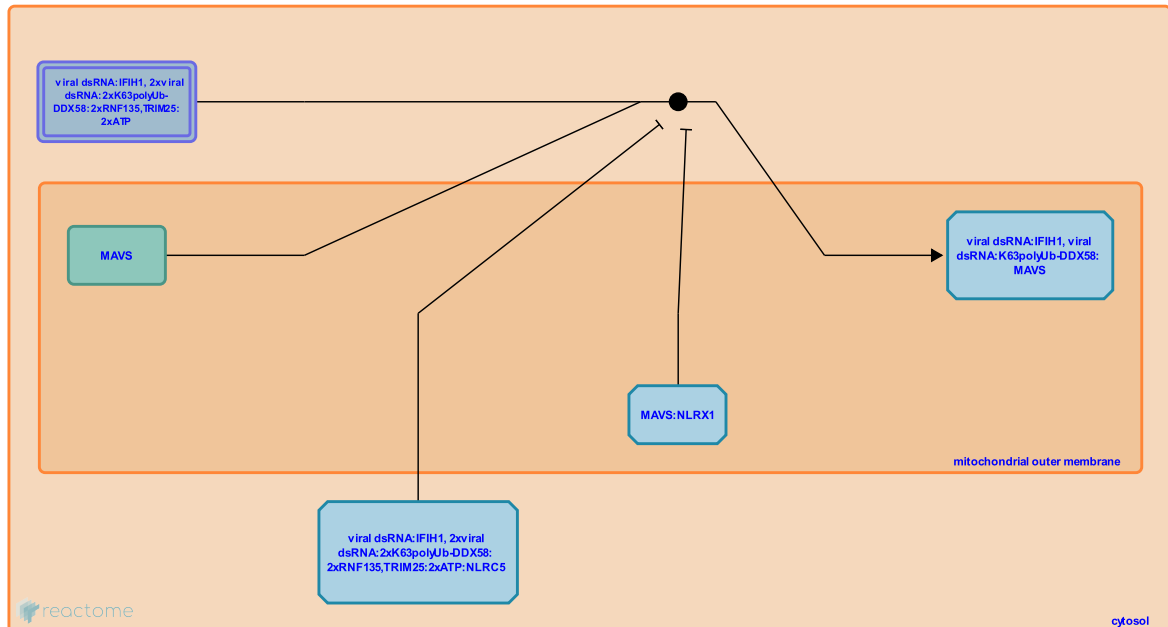
viral dsRNA:IFIH1, viral dsRNA:K63polyUb-DDX58 bind MAVS ↗

Location: DDX58/IFIH1-mediated induction of interferon-alpha/beta

Stable identifier: R-HSA-168909

Type: binding

Compartments: cytosol, mitochondrial outer membrane



NLRC5 competes with IPS-1 for binding to the CARD domain of RIG-I/MDA5. NLRC5 specifically recognize the CARD domains of RIG-I/MDA5 when the CARD domains become accessible after viral infection, leading to dampened activation of IRF3.

NLRX1 is a member of nucleotide-binding domain and leucine-rich repeat containing (NLR) protein family. NLRX1 competes with RIG-I for IPS-1 interaction and has been identified as a negative regulator of RLR signaling. NLRX1 resides at the outer mitochondrial membrane where IPS-1 is located and this interaction is mediated by the CARD region of IPS-1 and a putative nucleotide-binding domain (NBD) of NLRX1. This interaction between NLRX1 and IPS-1 prevents the association between RIG-I/MDA5 and IPS-1.

Upon binding viral dsRNA, Probable ATP-dependent RNA helicase DDX58 (DDX58, RIG-I, RIG-1) and Interferon-induced helicase C domain-containing protein 1 (IFIH1, MDA5) recruit the downstream signal transducer Mitochondrial antiviral-signaling protein (MAVS, IPS-1). This mitochondria-bound adaptor has an N-terminal CARD-like domain (CLD) which associates with the CARD regions of DDX58 and IFIH1 to mediate induction of interferons.

Preceded by: DDX58 is K63 polyubiquitinated, viral dsRNA binds IFIH1:TKFC

Literature references

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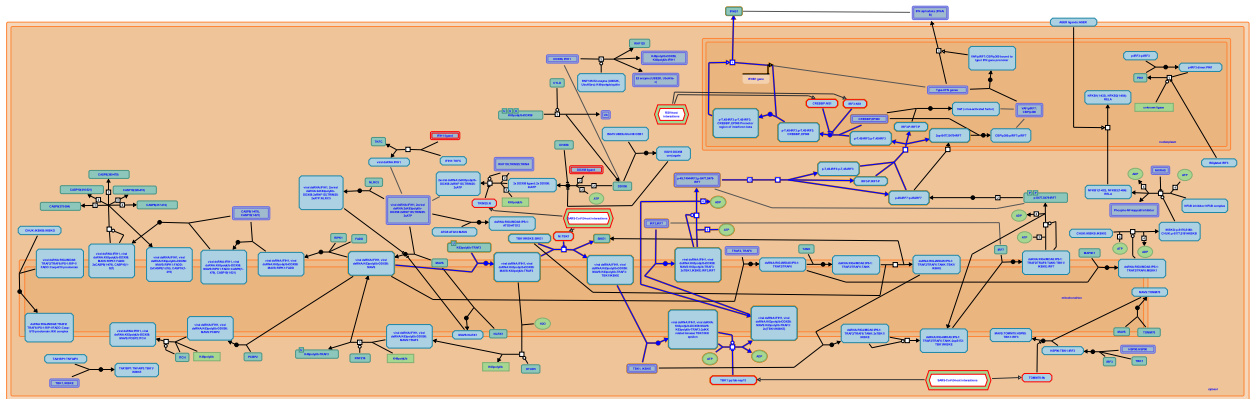
Akira, S., Kawai, T.

TRAF3-dependent IRF activation pathway ↗

Location: DDX58/IFIH1-mediated induction of interferon-alpha/beta

Stable identifier: R-HSA-918233

Compartments: mitochondrial outer membrane



reactome

MAVS via its TRAF-interaction motif (TIM) directly interacts with TRAF3 and recruits TRAF3 to the signaling complex. TRAF3 acts as a scaffold for the assembly of a signaling complex composed of IKK epsilon/TBK1, leading to the activation of transcription factors IRF3/IRF7.

Literature references

Perry, A., Saha, SK., Oganessian, 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. ↗

Kawai, T., Akira, S. (2007). Antiviral signaling through pattern recognition receptors. *J Biochem*, 141, 137-45. ↗

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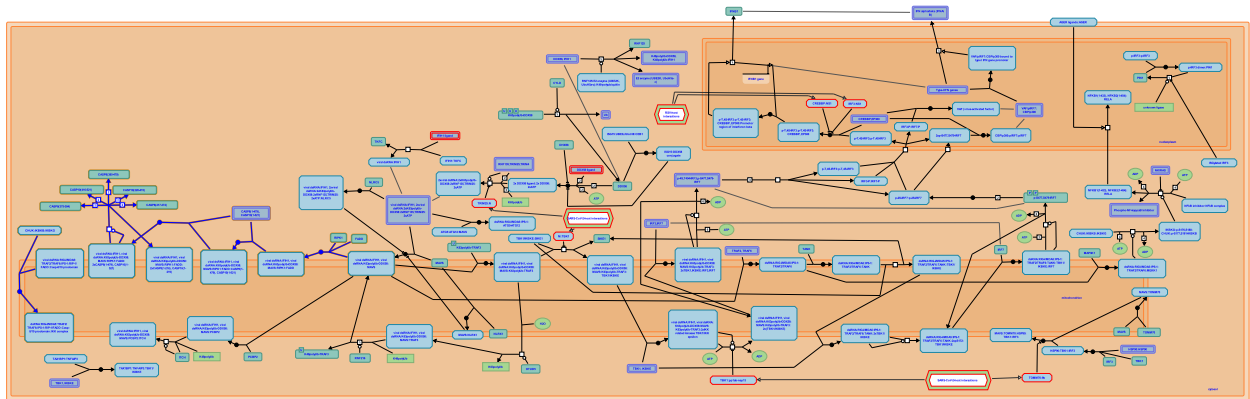
2010-08-02	Authored, Edited	Garapati, P V.
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NF- κ B activation through FADD/RIP-1 pathway mediated by caspase-8 and -10 ↗

Location: DDX58/IFIH1-mediated induction of interferon-alpha/beta

Stable identifier: R-HSA-933543

Compartments: mitochondrial outer membrane



reactome

Fas-AssociatedDeathDomain (FADD) and receptor interacting protein 1 (RIP1) are death domain containing molecules that interact with the C-terminal portion of IPS-1 and induce NF- κ B through interaction and activation of initiator caspases (caspase-8 and -10). Caspases are usually involved in apoptosis and inflammation but they also exhibit nonapoptotic functions. These nonapoptotic caspase functions involve prodomain-mediated activation of NF- κ B. Processed caspases (caspase-8/10) encoding the DED (death effector domain) strongly activate NF- κ B. The exact mechanism by which caspases mediate NF- κ B activation is unclear, but the prodomains of caspase-8/10 may act as a scaffolding and allow the recruitment of the IKK complex in association with other signaling molecules.

Literature references

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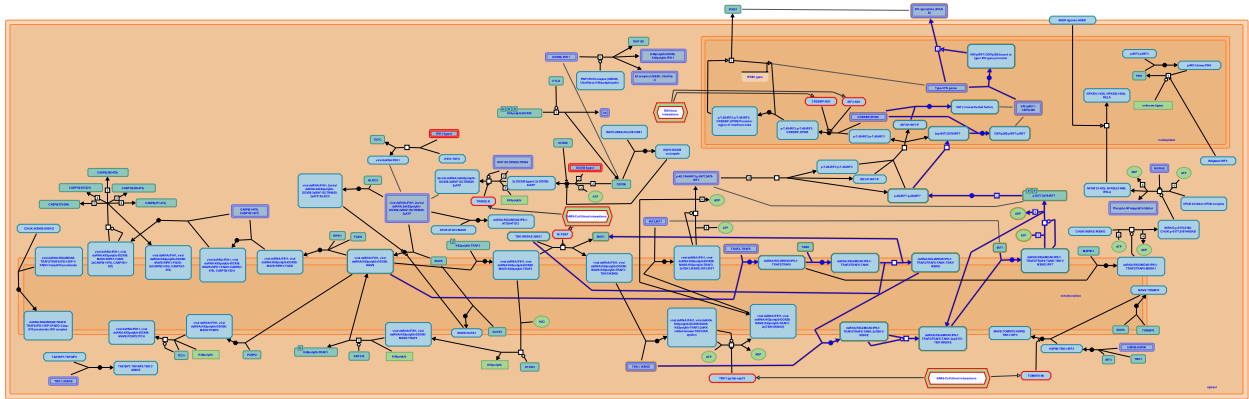
2010-08-02	Authored, Edited	Garapati, P V.
2010-10-30	Reviewed	Akira, S., Kawai, T.

TRAF6 mediated IRF7 activation ↗

Location: DDX58/IFIH1-mediated induction of interferon-alpha/beta

Stable identifier: R-HSA-933541

Compartments: mitochondrial outer membrane



reactome

TRAF6 is crucial for both RIG-I- and MDA5-mediated antiviral responses. The absence of TRAF6 resulted in enhanced viral replication and a significant reduction in the production of type I IFNs and IL6 after infection with RNA virus. Activation of NF- κ B and IRF7, but not that of IRF3, was significantly impaired during RIG-like helicases (RLHs) signaling in the absence of TRAF6. TRAF6-induced activation of IRF is likely to be specific for IRF7, while TRAF3 is thought to activate both IRF3 and IRF7. These results strongly suggest that the TRAF6- and TRAF3-dependent pathways are likely to bifurcate at IPS-1, but to converge later at IRF7 in order to co-operatively induce sufficient production of type I IFNs during RLH signaling.

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. ↗

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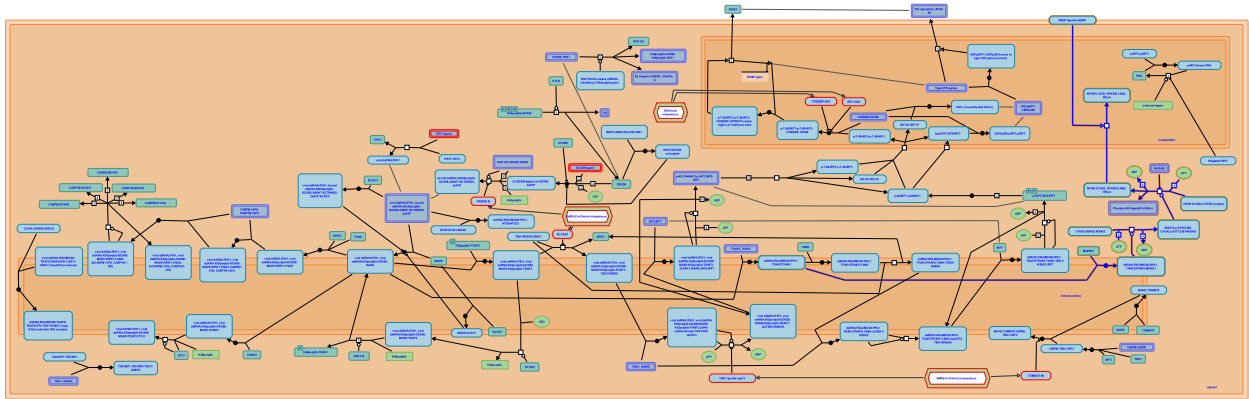
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TRAF6 mediated NF-kB activation ↗

Location: DDX58/IFIH1-mediated induction of interferon-alpha/beta

Stable identifier: R-HSA-933542

Compartments: cytosol, mitochondrial outer membrane



reactome

The TRAF6/TAK1 signal activates a canonical IKK complex, resulting in the activation of NF-kB as well as MAPK cascades leading to the activation of AP-1. Although TRAF6/TAK1 has been implicated in Toll like receptor (TLR) mediated cytokine production, the involvement of these molecules in the regulation of type I IFN induction mediated by RIG-I/MDA5 pathway is largely unknown. According to the study done by Yoshida et al RIG-I/IPS-1 pathway requires TRAF6 and MAP3K, MEKK1 to activate NF-kB and MAP Kinases for optimal induction of type I IFNs.

Literature references

Kobayashi, T., Kawai, T., Yoshioka, T., Yoshida, H., Takaesu, G., Yoshida, R. et al. (2008). TRAF6 and MEKK1 play a pivotal role in the RIG-I-like helicase antiviral pathway. *J Biol Chem*, 283, 36211-20. ↗

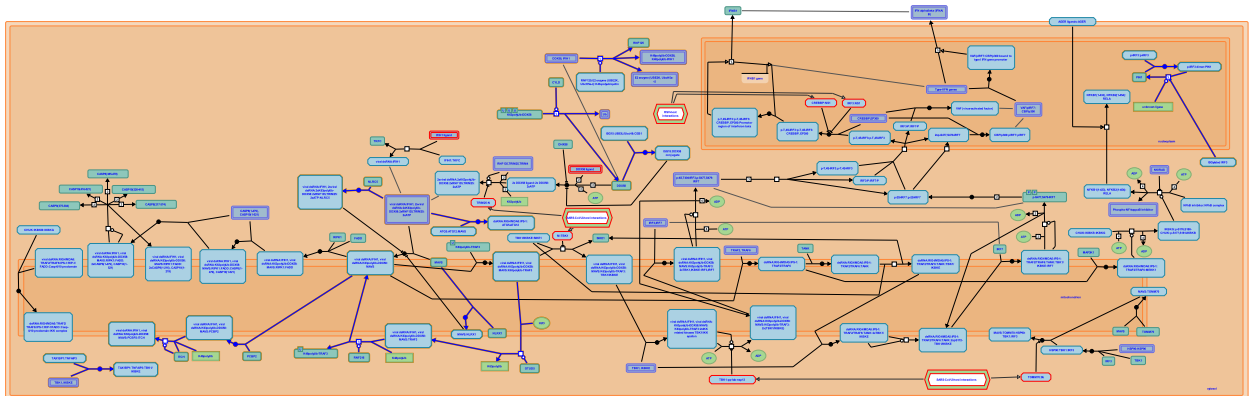
Editions

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Negative regulators of DDX58/IFIH1 signaling ↗

Location: DDX58/IFIH1-mediated induction of interferon-alpha/beta

Stable identifier: R-HSA-936440



reactome

As with other cytokine systems, production of type I IFN is a transient process, and can be hazardous to the host if unregulated, resulting in chronic cellular toxicity or inflammatory and autoimmune diseases. RIG-I-mediated production of IFN can, in turn, increase the transcription of RIG-I itself, thus setting into motion an IFN amplification loop, which if left unchecked, could become deleterious to the host. This module mainly focuses on the endogenous negative regulation of the RIG-I-like receptor (RLR) family proteins RIG-I and MDA5.

Literature references

Ting, JP., Moore, CB. (2008). Regulation of mitochondrial antiviral signaling pathways. *Immunity*, 28, 735-9. ↗

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

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2010-10-30	Reviewed	Akira, S., Kawai, T.

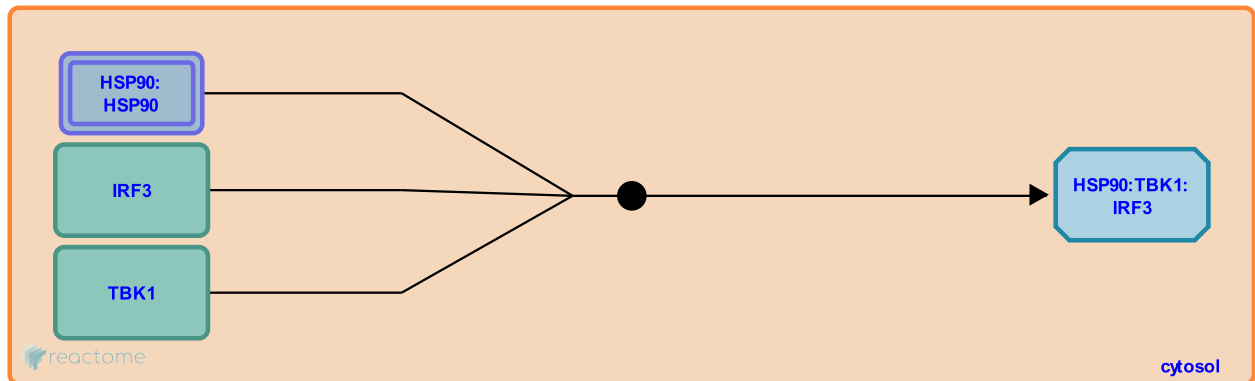
HSP90 binds TBK1 and IRF3 ↗

Location: [DDX58/IFIH1-mediated induction of interferon-alpha/beta](#)

Stable identifier: R-HSA-9709831

Type: binding

Compartments: cytosol



During viral infection, cytosolic viral RNA triggers activation of mitochondrial antiviral-signaling protein (MAVS) and the formation of MAVS signalosome (Kawai T et al. 2005; Seth RB et al. 2005; Xu LG et al. 2005). Activated MAVS recruits TANK-binding kinase 1 (TBK1), interferon regulatory factor 3 (IRF3) and IRF7 to the mitochondria leading to the activation of IRF3/IRF7 and subsequent production of type I interferons (Kawai T et al. 2005; Seth RB et al. 2005; Xu LG et al. 2005).

Co-immunoprecipitation assay showed that both TBK1 and IRF3 associated with heat shock protein 90kDa (HSP90), which facilitated signal transduction from TBK1 to IRF3 in Sendai virus (SeV)-infected human embryonic kidney (HEK293) cells (Yang K et al. 2006). MAVS, TBK1 and IRF3 were found to associate with mitochondrial import receptor subunit TOM70 (TOMM70) in HEK293 cells (Liu XY et al. 2010). TOMM70 localizes on the outer membrane of the mitochondria to mediate the translocation of mitochondrial protein precursors from the cytosol into the mitochondria (reviewed in Fan AC & Young JC 2011; Sokol AM et al. 2014; Kreimendahl S & Rassow J 2020). The molecular chaperone complexes of HSP90 and HSP70 were shown to deliver precursor proteins to TOMM70 for subsequent import (Young JC et al. 2003; Zanphorlin LM et al. 2016). The C-terminal motif (EEVD) of HSP90 was found to bind the N-terminal TPR clamp-type domain of TOMM70 (Liu XY et al. 2010; Gava LM et al. 2011). Knockdown of HSP90 by small interfering RNA (siRNA) decreased the association of TOMM70 with TBK1 and IRF3 in HEK293T cells (Liu XY et al. 2010). Further, in SeV-stimulated HEK293 cells, cytosolic BAX translocated to the mitochondrial outer membrane and induced apoptosis in the IRF3-dependent manner via the formation of the TOMM70:HSP90:IRF3:BAX protein complex (Wei B et al. 2015). The data suggest that HSP90 forms a complex with TBK1 and IRF3 in the cytosol and deliver them to the MAVS signalosome on the mitochondria.

Interaction between HSP90 and US11, a viral protein derived from human herpesvirus 1 (HHV-1, also known as herpes simplex virus 1, HSV-1) disrupted the formation of the HSP90:TBK1:IRF3 complex and induced degradation of TBK1 through a proteasome-dependent pathway in mouse embryonic fibroblasts (MEFs) (Liu X et al. 2018).

Followed by: [MAVS:TOMM70 recruits HSP90:TBK1:IRF3](#)

Literature references

Wang, C., Sun, S., Yang, K., Tang, Y., Zhang, B., Qi, R. et al. (2006). Hsp90 regulates activation of interferon regulatory factor 3 and TBK-1 stabilization in Sendai virus-infected cells. *Mol Biol Cell*, 17, 1461-71. ↗

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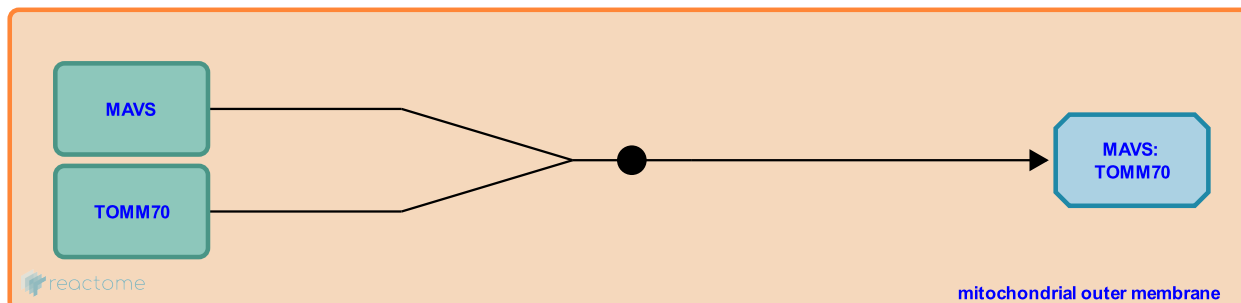
MAVS binds TOMM70 ↗

Location: [DDX58/IFIH1-mediated induction of interferon-alpha/beta](#)

Stable identifier: R-HSA-9709842

Type: binding

Compartments: mitochondrial outer membrane



Mitochondrial import receptor subunit TOM70 (TOMM70) recognizes mitochondrial protein precursors in the cytosol and mediates their transition to the mitochondrial compartments (reviewed in Fan ACY & Young JC et al. 2011; Sokol AM et al. 2014; Kreimendahl S & Rassow J 2020). The molecular chaperone complexes of heat shock protein 90 kDa (HSP90) and HSP70 deliver precursor proteins to TOMM70 for subsequent import (Young JC et al. 2003; Zanphorlin LM et al. 2016).

During viral infection, cytosolic viral RNA triggers activation of mitochondrial antiviral-signaling protein (MAVS) and the formation of MAVS signalosome (Kawai T et al. 2005; Seth RB et al. 2005; Xu LG et al. 2005). MAVS localizes on the outer membrane of mitochondria through its C-terminal transmembrane (TM) domain. Activated MAVS recruits TANK-binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3) to mitochondria leading to the activation of IRF3 and subsequent production of type I interferons.

Immunoprecipitation assays coupled to mass spectrometry analysis revealed that TOMM70 interacted with exogenously expressed MAVS in Sendai virus (SeV)-stimulated human embryonic kidney (HEK293) cells (Liu XY et al. 2010). The TM domains of both MAVS and TOMM70 were required for their interaction. In addition, TOMM70 interacted strongly with the C-terminal motif (EEVD) of HSP90 (Liu XY et al. 2010; Gava LM et al. 2011). TOMM70 also co-immunoprecipitated with TBK1 and IRF3 in HEK293 cells (Liu XY et al. 2010). Further, both TBK1 and IRF3 were found to associate with HSP90, which facilitated signal transduction from TBK1 to IRF3 in SeV-infected HEK293 cells (Yang K et al. 2006). Moreover, SeV infection enhanced the interaction between IRF3 and apoptosis regulator BAX (BAX) in HEK293T cells (Wei B et al. 2015). In SeV-stimulated HEK293 cells, cytosolic BAX translocated to the mitochondrial outer membrane and induced apoptosis in the IRF3-dependent manner via the formation of the TOMM70:HSP90:IRF3:BAX protein complex (Wei B et al. 2015). Knockdown of HSP90 by small interfering RNA (siRNA) decreased the association of TOMM70 with TBK1 and IRF3 (Liu XY et al. 2010). Overexpression of TOMM70 enhanced mRNA levels of IRF3-responsive genes (including IFNB, IFIT1 and RANTES) in HEK293 cells during SeV infection or poly(I:C) stimulation, whereas knockdown of TOMM70 by siRNA showed an inhibitory effect. Similar results were obtained in murine bone marrow-derived macrophages and bone marrow-derived dendritic cells (Liu XY et al. 2010). Thus, the association of MAVS with TOMM70 is thought to potentiate the HSP90-mediated recruitment of TBK1 and IRF3 to mitochondria during viral infection thereby inducing IRF3-mediated host antiviral responses. In addition, binding of MAVS to TOMM70 can also trigger BAX-dependent apoptosis (Wei B et al. 2015). TOMM70 also associated with TRADD, TRAF6 and STING in HEK293 cells, further indicating that TOMM70 is a component of MAVS signal complex on mitochondria (Liu XY et al. 2010).

The viral orf9b (9b) proteins derived from SARS-CoV-1 and SARS-CoV-2 inhibit the MAVS-mediated production of type I IFNs by targeting TOMM70 on the mitochondria (Jiang HW et al. 2020).

This Reactome event shows the association of MAVS with TOMM70.

Followed by: [MAVS:TOMM70 recruits HSP90:TBK1:IRF3](#)

Literature references

Wang, C., Shi, HX., Liu, XY., Shan, YF., Wei, B. (2010). Tom70 mediates activation of interferon regulatory factor 3 on mitochondria. *Cell Res*, 20, 994-1011. [↗](#)

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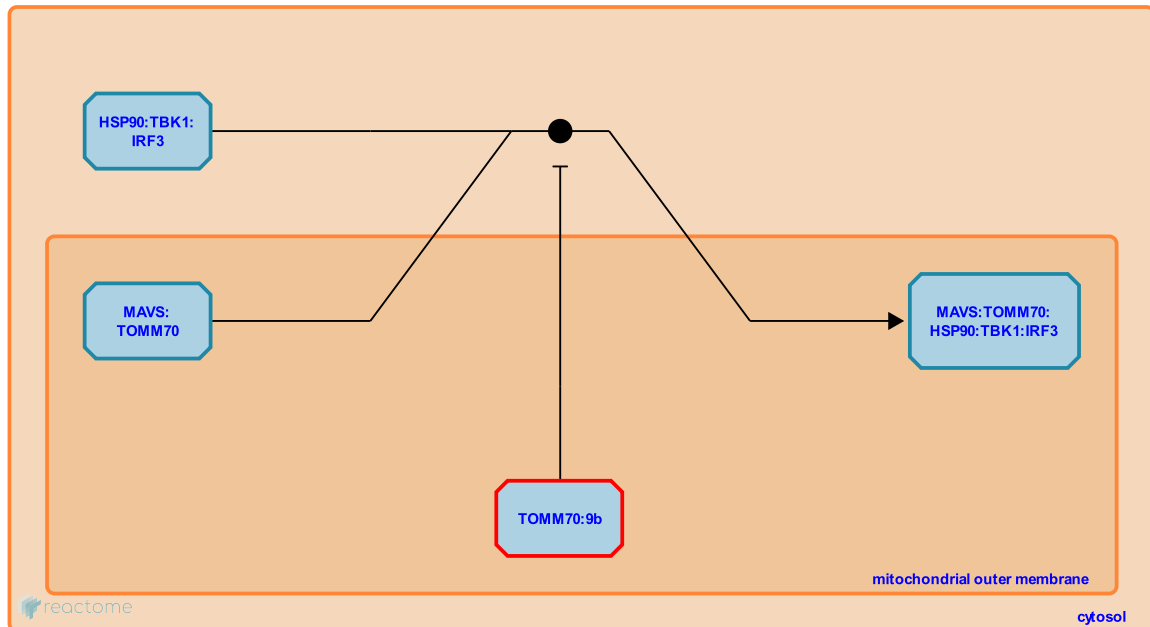
MAVS:TOMM70 recruits HSP90:TBK1:IRF3 ↗

Location: [DDX58/IFIH1-mediated induction of interferon-alpha/beta](#)

Stable identifier: R-HSA-9709852

Type: binding

Compartments: cytosol, mitochondrial outer membrane



Mitochondrial import receptor subunit TOM70 (TOMM70) recognizes mitochondrial protein precursors in the cytosol and mediates their translocation to the mitochondrial compartments (reviewed in Fan ACY & Young JC et al. 2011; Sokol AM et al. 2014; Kreimendahl S & Rassow J 2020). The molecular chaperone complexes of heat shock protein 90 kDa (HSP90) and HSP70 were shown to deliver precursor proteins to TOMM70 for subsequent import (Young JC et al. 2003; Zanphorlin LM et al. 2016). Mitochondrial import receptor subunit TOM20 (TOMM20) competes with HSC70 (HSPA8) and HSP90 for TOMM70 binding (Fan ACY et al. 2011).

During viral infection, cytosolic viral RNA triggers activation of mitochondrial antiviral-signaling protein (MAVS) and the formation of MAVS signalosome (Kawai T et al. 2005; Seth RB et al. 2005; Xu LG et al. 2005). MAVS localizes on the outer membrane of mitochondria through its C-terminal transmembrane (TM) domain. Activated MAVS recruits TANK-binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3) to mitochondria leading to the activation of IRF3 and subsequent production of type I interferons. MAVS activates TBK1 in the TNF receptor-associated factors (TRAF)-dependent manner (Liu S et al. 2013; Fang R et al. 2017). Further, NF-kappa-B essential modulator (NEMO) links TBK1 to MAVS via TANK (Zhao T et al. 2007; Fang R et al. 2017).

Immunoprecipitation assays coupled to mass spectrometry analysis revealed that TOMM70 interacted with exogenously expressed MAVS in Sendai virus (SeV)-stimulated human embryonic kidney (HEK293) cells (Liu XY et al. 2010). The TM domains of both MAVS and TOMM70 were required for their interaction. In addition, TOMM70 interacted strongly with the C-terminal motif (EEVD) of HSP90 (Liu XY et al. 2010; Gava LM et al. 2011). TOMM70 also co-immunoprecipitated with TBK1 and IRF3 in HEK293 cells (Liu XY et al. 2010). Further, both TBK1 and IRF3 associated with HSP90, which facilitated signal transduction from TBK1 to IRF3 in SeV-infected HEK293 cells (Yang K et al. 2006). Moreover, SeV infection enhanced the interaction between IRF3 and apoptosis regulator BAX (BAX) in HEK293T cells (Wei B et al. 2015). In SeV-stimulated HEK293 cells, cytosolic BAX translocated to the mitochondrial outer membrane and induced apoptosis in the IRF3-dependent manner via the formation of the TOMM70:HSP90:IRF3:BAX protein complex (Wei B et al. 2015). Knockdown of HSP90 by small interfering RNA (siRNA) decreased the association of TOMM70 with TBK1 and IRF3 (Liu XY et al. 2010). Overexpression of TOMM70 enhanced mRNA levels of IRF3-responsive genes (including IFNB, IFIT1 and RANTES) in HEK293 cells during SeV infection or poly(I:C) stimulation, whereas knockdown of TOMM70 by siRNA showed an inhibitory effect. Similar results were obtained in murine bone marrow-derived macrophages (BMDM) and bone marrow-derived dendritic cells (BMDC) (Liu XY et al. 2010). Thus, the association of MAVS with TOMM70 is thought to potentiate the HSP90-mediated recruitment of TBK1 and IRF3 to mitochondria during viral infection thereby inducing IRF3-mediated host antiviral responses.

SARS-CoV-2 9b interaction with TOMM70 inhibits binding of HSP90 to TOMM70 (Jiang HW et al. 2020).

Preceded by: [MAVS binds TOMM70](#), [HSP90 binds TBK1 and IRF3](#)

Literature references

Wang, C., Sun, S., Yang, K., Tang, Y., Zhang, B., Qi, R. et al. (2006). Hsp90 regulates activation of interferon regulatory factor 3 and TBK-1 stabilization in Sendai virus-infected cells. *Mol Biol Cell*, 17, 1461-71. [↗](#)

Wang, C., Shi, HX., Liu, XY., Shan, YF., Wei, B. (2010). Tom70 mediates activation of interferon regulatory factor 3 on mitochondria. *Cell Res*, 20, 994-1011. [↗](#)

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