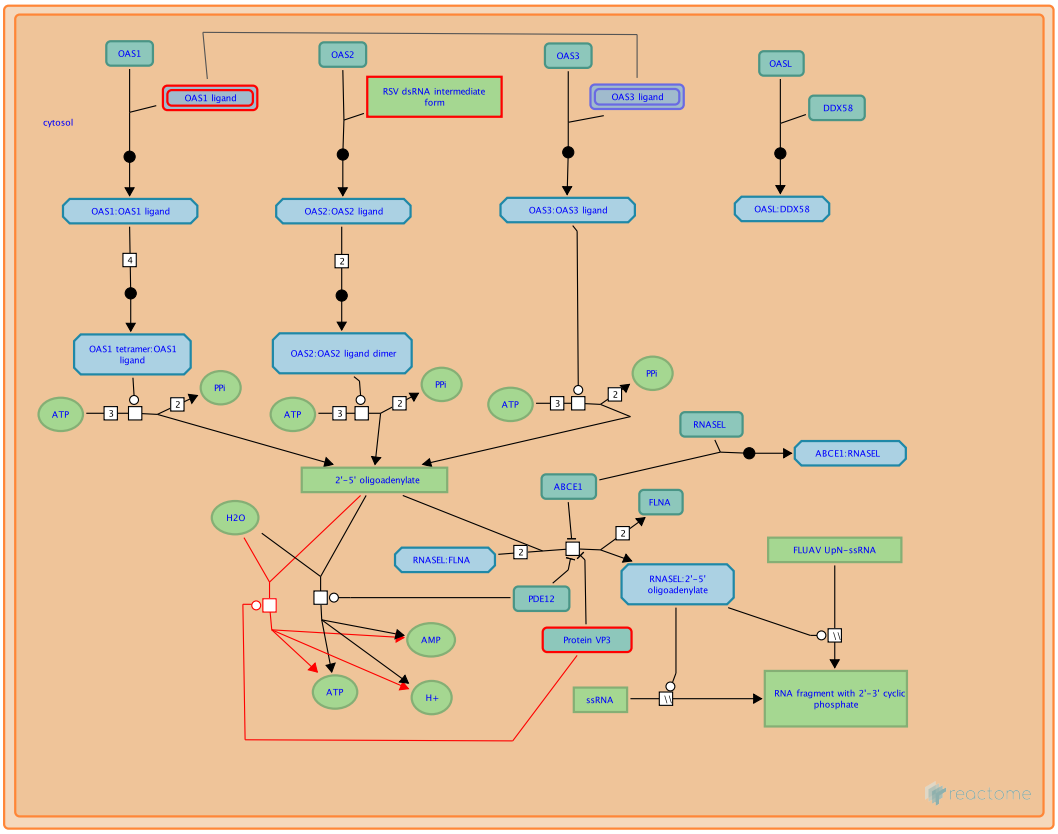
OAS antiviral response



D'Eustachio, P., Shamovsky, V., Silverman, RH.

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

20/09/2021

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. ↗

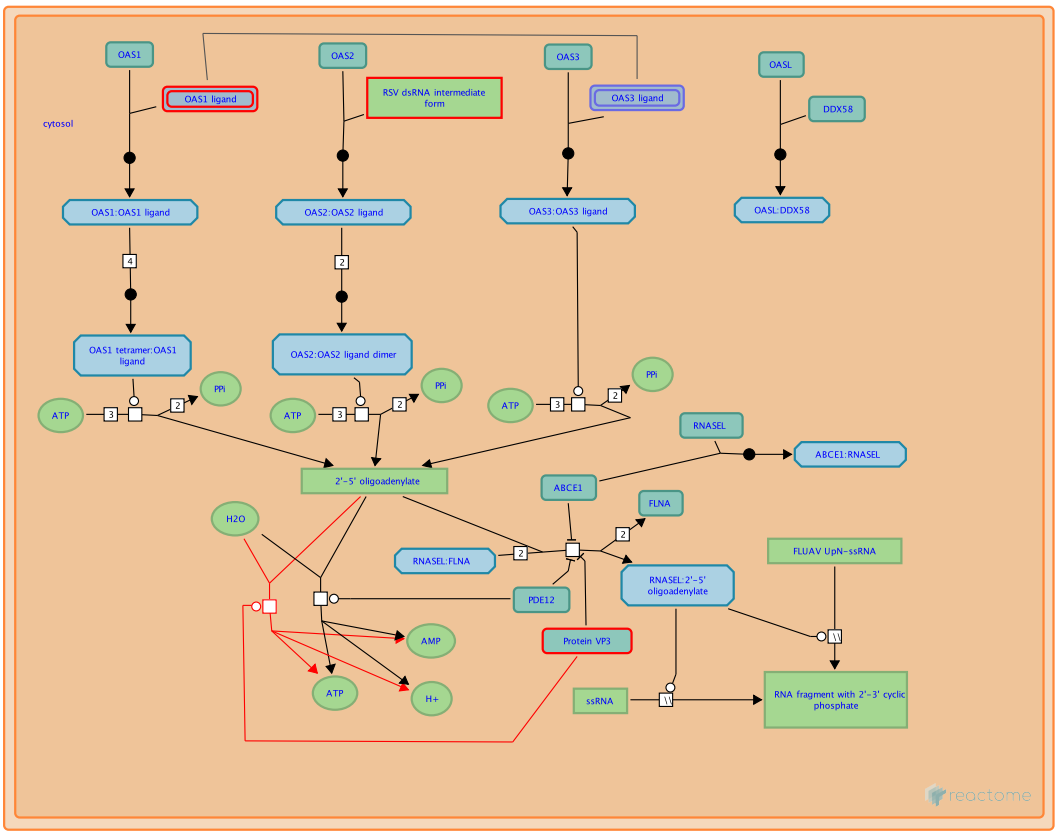
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

OAS antiviral response ↗

Stable identifier: R-HSA-8983711

Compartments: cytosol



The human oligoadenylate synthetase (OAS) family consists of four proteins whose production is stimulated by interferon, OAS1, OAS2, OAS3, and OASL. The first three members have the 2'-5'-oligoadenylate synthetase activity for which the family is named (Sadler AJ & Williams BR 2008), whereas OASL is devoid of this activity despite sharing significant sequence similarity with the other OAS proteins (Zhu J et al. 2015). OAS1, 2, and 3 are activated by double-stranded RNA to synthesize 5'-triphosphorylated 2'-5'-oligoadenylates (2-5A) from ATP (Kerr IM & Brown RE 1978). The 2-5A serve as chemically unique second messengers that induce regulated RNA decay by activating ribonuclease L (RNase L), thus mediating antiviral innate immunity (Zhou A et al. 1993; Lin RJ et al. 2009; Huang H et al. 2014; Han Y et al. 2014). RNase L has also been implicated in antibacterial innate immunity (Li XL et al. 2008). RNase L cleaves single-stranded RNA (ssRNA) in U-rich sequences, typically after UU or UA dinucleotides leaving a 5'-OH and 2',3'-cyclic phosphate (Floyd-Smith G et al. 1981; Wreschner DH et al.1981; Cooper DA et al. 2014).

Some OAS proteins have additional or alternative antiviral functions that are independent of RNase L activity (Perelygin AA et al., 2002; Kristiansen H et al. 2011). The precise mechanisms of RNase L-independent OAS antiviral activities remain to be fully elucidated.

Literature references

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

Tanaka, N., Nakanishi, M., Kusakabe, Y., Goto, Y., Kitade, Y., Nakamura, KT. (2005). Molecular basis for recognition of 2',5'-linked oligoadenylates by the N-terminal ankyrin repeat domain of human ribonuclease L. *Nucleic Acids Symp Ser (Oxf)*, 323-4. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

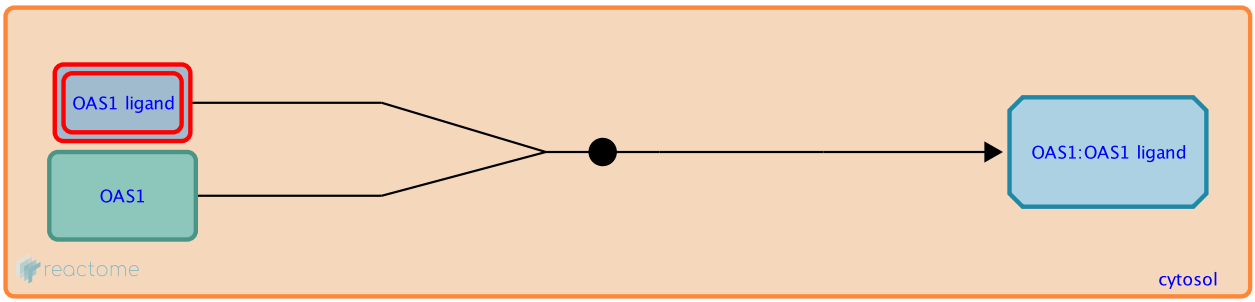
OAS1 binds viral dsRNA ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8983671

Type: binding

Compartments: cytosol



Human oligoadenylate synthetase 1 (OAS1) recognizes double-stranded RNA (dsRNA) typically produced by viral infections. The X-ray crystal structure of human OAS1 bound to a model 18-bp dsRNA duplex revealed that dsRNA binding allosterically drives a functionally essential structural reorganization within human OAS1 that narrows the adenosine triphosphate (ATP)-binding cleft and repositions a catalytic residue to complete its active site (Donovan J et al. 2013). Once stimulated by dsRNA, OAS1 uses ATP to synthesize a series of 5'-triphosphorylated 2'-5'-linked oligoadenylates containing 2 to greater than 5 adenylyl residues. The 5'-triphosphorylated 2'-5'-linked triadenylate (i.e., ppp5'A2'p5'A2'p5'A) is typically the most abundant active species (Kerr IM & Brown RE 1978).

Followed by: OAS1 oligomerizes

Literature references

Donovan, J., Dufner, M., Korennykh, A. (2013). Structural basis for cytosolic double-stranded RNA surveillance by human oligoadenylate synthetase 1. *Proc. Natl. Acad. Sci. U.S.A., 110*, 1652-7. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

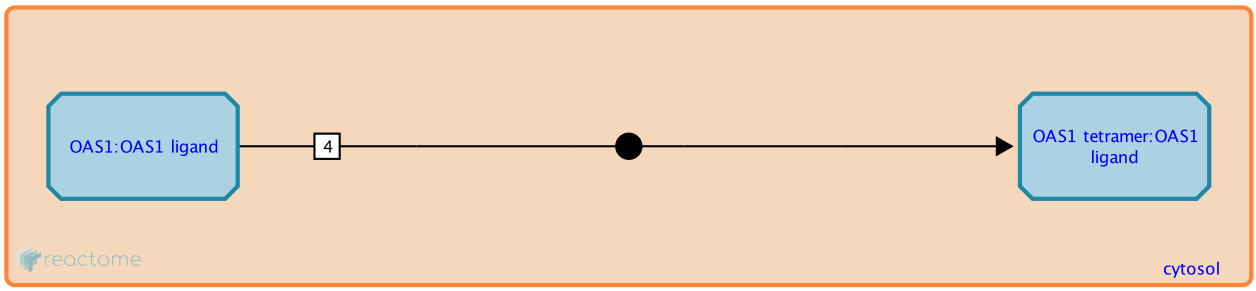
OAS1 oligomerizes ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8983688

Type: binding

Compartments: cytosol



The tetramerization of 2'-5'-oligoadenylate synthetase OAS1 is required for enzymatic activity (Ghosh A et al. 1997).

Preceded by: OAS1 binds viral dsRNA

Followed by: OAS1 produces oligoadenylates

Literature references

Ghosh, A., Sarkar, SN., Guo, W., Bandyopadhyay, S., Sen, GC. (1997). Enzymatic activity of 2'-5'-oligoadenylate synthetase is impaired by specific mutations that affect oligomerization of the protein. *J. Biol. Chem., 272*, 33220-6. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

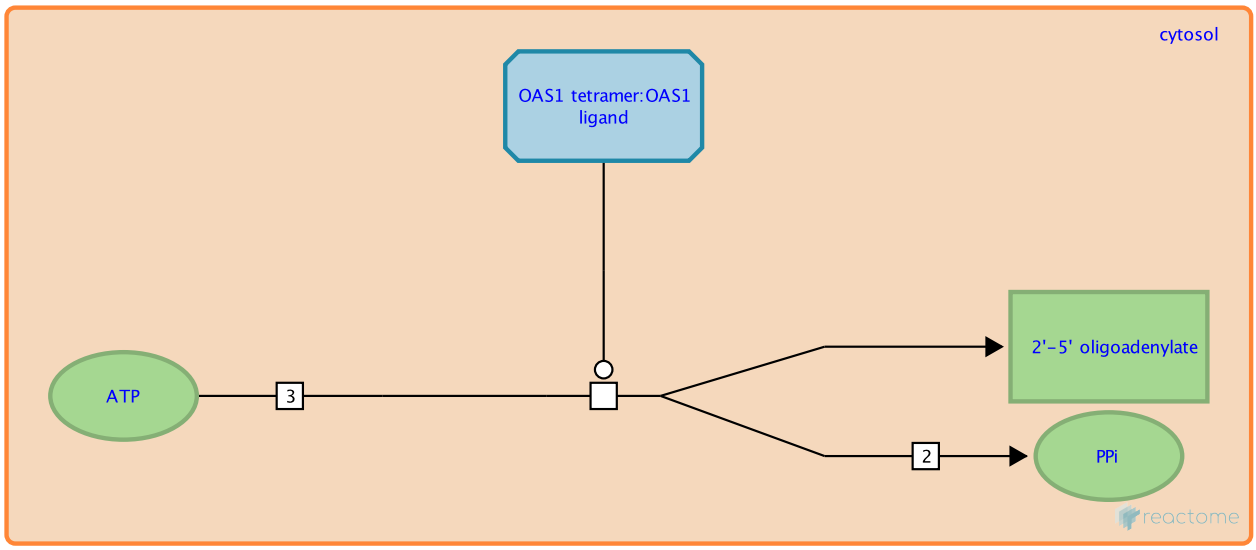
OAS1 produces oligoadenylates ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8983680

Type: transition

Compartments: cytosol



Oligoadenylate synthetase 1 (OAS1) produces the second messenger 5'-triphosphorylated 2'-5'-oligoadenylate (2-5A), which limits viral propagation through the activation of the enzyme RNase L (reviewed by Silverman RH 2007; Hornung V et al. 2014). OAS1 produces 2-5A from ATP by transferring an AMP unit from the AMP donor substrate (ATP) to the 2'-hydroxyl group of an AMP acceptor substrate, ATP or a preformed 2-5A oligomer (Lohofener J et al. 2015). This produces a 2-5A dimer (ppp5'A(2'-5')A) or an elongated 2-5A oligomer (ppp5'A((2'-5')A)n), as well as one molecule of pyrophosphate (PPi) for each AMP residue added (Lohofener J et al. 2015). Structural studies showed that RNA-induced conformational rearrangement in OAS1 positions the active site residues D75, D77, and D148 compactly for coordination of two Mg2+ ions and for binding of ATP (Donovan J et al. 2013). The assembly of this critical active-site structure of OAS1 provides the gate that couples binding of dsRNA to the production and downstream functions of 2-5A, enabling OAS1 to function as a sensor of double-stranded RNA (dsRNA) (Donovan J et al. 2013).

Preceded by: OAS1 oligomerizes

Followed by: RNASEL binds 2'-5' oligoadenylate

Literature references

Donovan, J., Dufner, M., Korennykh, A. (2013). Structural basis for cytosolic double-stranded RNA surveillance by human oligoadenylate synthetase 1. *Proc. Natl. Acad. Sci. U.S.A., 110*, 1652-7. ↗

Lohöfener, J., Steinke, N., Kay-Fedorov, P., Baruch, P., Nikulin, A., Tishchenko, S. et al. (2015). The Activation Mechanism of 2'-5'-Oligoadenylate Synthetase Gives New Insights Into OAS/cGAS Triggers of Innate Immunity. *Structure, 23*, 851-62. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

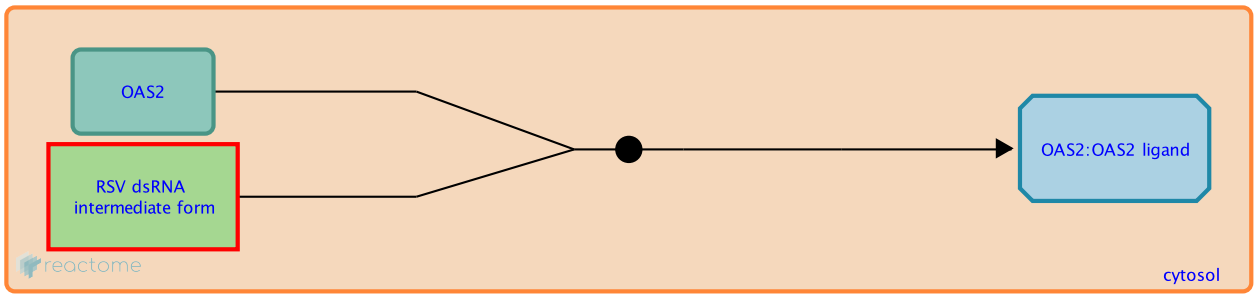
OAS2 binds viral dsRNA ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8985138

Type: binding

Compartments: cytosol



The human oligoadenylate synthetase 2 (OAS2) is activated by double-stranded RNA (dsRNA) (Hovanessian AG et al. 1988; Behera AK et al. 2002; Kristiansen H et al. 2011).

Followed by: OAS2 dimerizes

Literature references

Hovanessian, AG., Svab, J., Marié, I., Robert, N., Chamaret, S., Laurent, AG. (1988). Characterization of 69- and 100-kDa forms of 2-5A-synthetase from interferon-treated human cells. *J. Biol. Chem., 263*, 4945-9. ↗

Sarkar, SN., Bandyopadhyay, S., Ghosh, A., Sen, GC. (1999). Enzymatic characteristics of recombinant medium isozyme of 2'-5' oligoadenylate synthetase. *J. Biol. Chem., 274*, 1848-55. ↗

Sarkar, SN., Miyagi, M., Crabb, JW., Sen, GC. (2002). Identification of the substrate-binding sites of 2'-5'-oligoadenylate synthetase. *J. Biol. Chem., 277*, 24321-30. ↗

Behera, AK., Kumar, M., Lockey, RF., Mohapatra, SS. (2002). 2'-5' Oligoadenylate synthetase plays a critical role in interferon-gamma inhibition of respiratory syncytial virus infection of human epithelial cells. *J. Biol. Chem., 277*, 25601-8. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

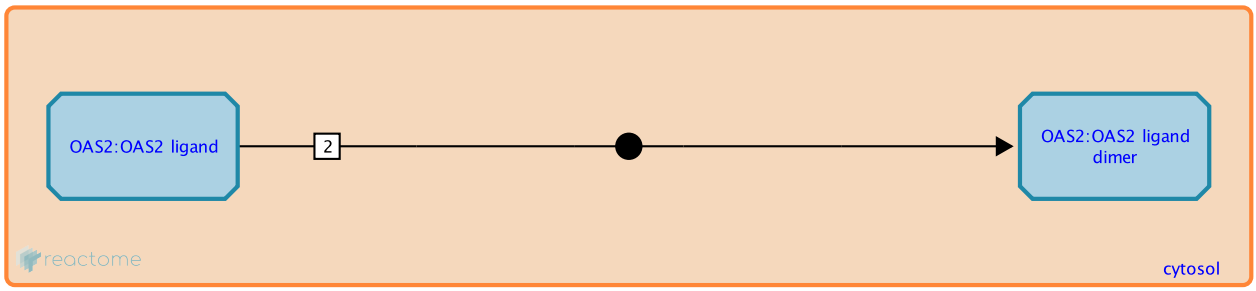
OAS2 dimerizes ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8985097

Type: binding

Compartments: cytosol



Gel filtration experiments using extracts from IFN-treated human HeLa and Daudi cells showed that 2',5'-oligoadenylate (2-5A) synthetase (OAS2, p69) exists as a dimer of 160 kDa (Marie I et al. 1990). Biochemical and mutational studies demonstrated that dimerization of OAS2 protein is required for its enzyme activity (Sarkar SN et al. 1999). Further, photo affinity cross-linking and peptide mapping to study the substrate binding sites in OAS2 have suggested that OAS2 is active only as a dimer because it catalyzes the joining of the acceptor substrate bound to one subunit to the donor substrate bound to the other subunit (Sarkar SN et al. 2002).

Preceded by: OAS2 binds viral dsRNA

Followed by: OAS2 produces oligoadenylates

Literature references

Ghosh, A., Sarkar, SN., Guo, W., Bandyopadhyay, S., Sen, GC. (1997). Enzymatic activity of 2'-5'-oligoadenylate synthetase is impaired by specific mutations that affect oligomerization of the protein. *J. Biol. Chem., 272*, 33220-6. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

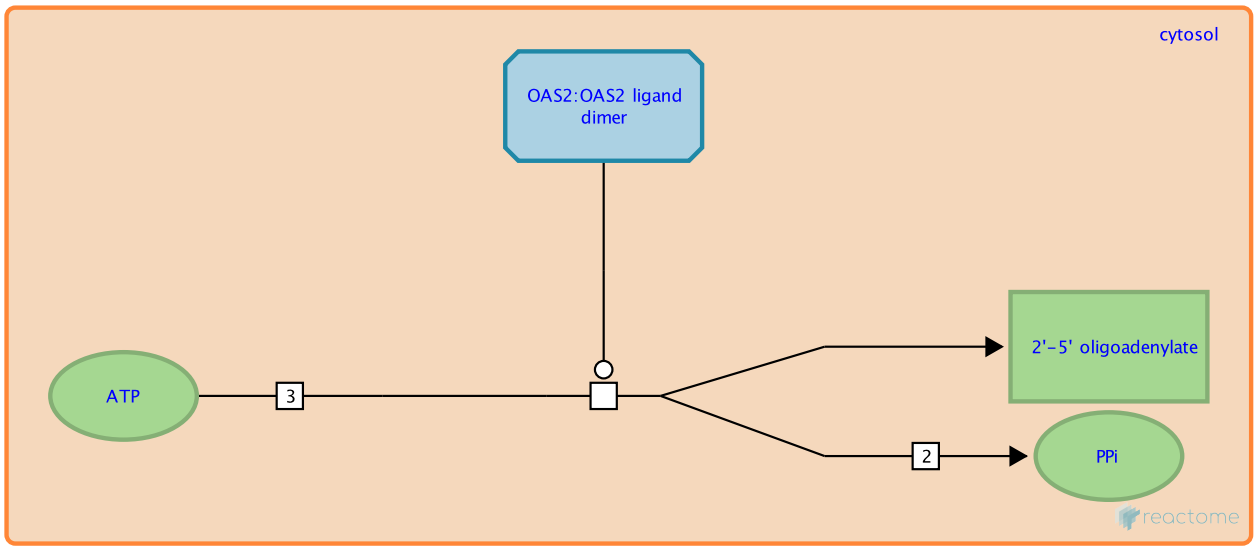
OAS2 produces oligoadenylates ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8985104

Type: transition

Compartments: cytosol



2'-5'-oligoadenylate synthetase 2 (OAS2) polymerizes ATP into 5'-triphosphorylated, 2'-5'-linked oligoadenylate (2-5A) (Hovanessian AG et al. 1988; Sarkar SN et al. 1999, 2002). 2-5A molecules are recognized by ribonuclease L (RNase L) (Han Y et al. 2014; Huang H et al. 2014). Activated RNase L cleaves viral and cellular RNA resulting in the inhibition of viral replication (Silverman RH 2007).

Preceded by: OAS2 dimerizes

Followed by: RNASEL binds 2'-5' oligoadenylate

Literature references

Hovanessian, AG., Svab, J., Marié, I., Robert, N., Chamaret, S., Laurent, AG. (1988). Characterization of 69- and 100-kDa forms of 2-5A-synthetase from interferon-treated human cells. *J. Biol. Chem., 263*, 4945-9. ↗

Sarkar, SN., Ghosh, A., Wang, HW., Sung, SS., Sen, GC. (1999). The nature of the catalytic domain of 2'-5'-oligoadenylate synthetases. *J. Biol. Chem., 274*, 25535-42. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

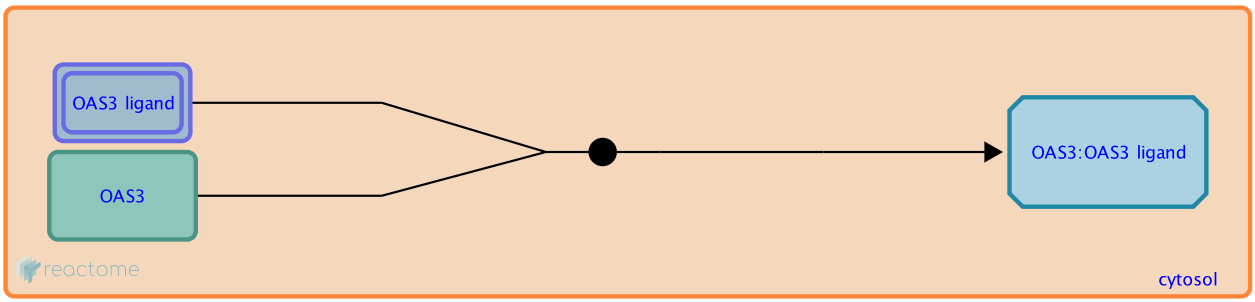
OAS3 binds viral dsRNA ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8985157

Type: binding

Compartments: cytosol



Viral dsRNA-activated oligoadenylate synthetase 3 (OAS3) exhibits a strong preference for long dsRNA. A study that included the crystal structure of the N-terminal enzymatically inactive 2'-5' oligoadenylate synthetase domain of human OAS3 (hOAS3.DI) in complex with 19-bp dsRNA indicated that this domain I (DI) subunit has high affinity for the binding of long (>50 bp) dsRNA, which then is presented to the enzymatically active C-terminal domain III (DIII) of OAS3 that produces 5’-triphosphorylated 2'-5' oligoadenylates from ATP (Donovan J et al. 2015). OAS3 was reported to be the major antiviral human OAS isoform (Li Y et al. 2016).

Followed by: OAS3 produces oligoadenylates

Literature references

Li, Y., Banerjee, S., Wang, Y., Goldstein, SA., Dong, B., Gaughan, C. et al. (2016). Activation of RNase L is dependent on OAS3 expression during infection with diverse human viruses. *Proc. Natl. Acad. Sci. U.S.A., 113*, 2241-6. ↗

Donovan, J., Whitney, G., Rath, S., Korennykh, A. (2015). Structural mechanism of sensing long dsRNA via a noncatalytic domain in human oligoadenylate synthetase 3. *Proc. Natl. Acad. Sci. U.S.A., 112*, 3949-54. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

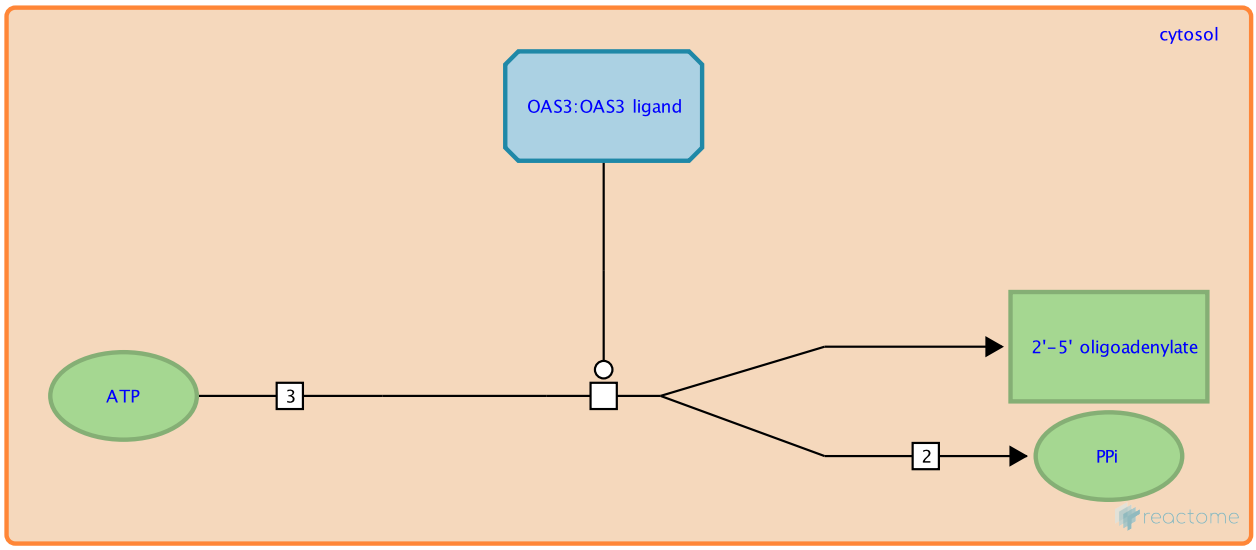
OAS3 produces oligoadenylates ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8985091

Type: transition

Compartments: cytosol



2'-5'-oligoadenylate synthetase 3 (OAS3) is a template-independent nucleotidyl transferase that, once activated by double-stranded RNA in the cytosol, produces second messenger molecules 5'-triphosphorylated 2',5'-linked oligoadenylates (2-5A). OAS3 was reported to produce preferentially dimeric 2-5A (Rebouillat D et al. 1999). However recent reports showed that OAS3 is able to synthesize 2',5'-oligoadenylates of sufficient length (the triadenylate and longer) to activate RNase L and thus limit viral propagation (Ibsen MS et al. 2014; Li Y et al. 2016).

Preceded by: OAS3 binds viral dsRNA

Followed by: RNASEL binds 2'-5' oligoadenylate

Literature references

Ibsen, MS., Gad, HH., Thavachelvam, K., Boesen, T., Desprès, P., Hartmann, R. (2014). The 2'-5'-oligoadenylate synthetase 3 enzyme potently synthesizes the 2'-5'-oligoadenylates required for RNase L activation. *J. Virol., 88*, 14222-31. ↗

Li, Y., Banerjee, S., Wang, Y., Goldstein, SA., Dong, B., Gaughan, C. et al. (2016). Activation of RNase L is dependent on OAS3 expression during infection with diverse human viruses. *Proc. Natl. Acad. Sci. U.S.A., 113*, 2241-6. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

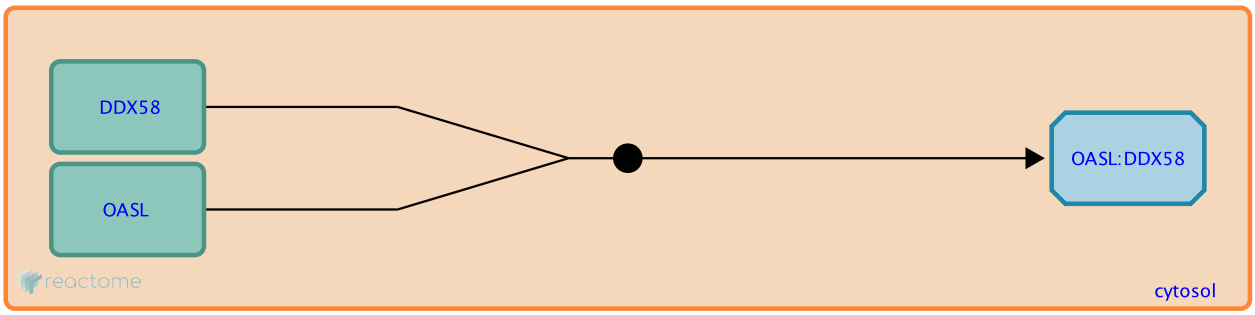
OASL binds DDX58 ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8985153

Type: binding

Compartments: cytosol



Interferon-dependent antiviral mechanisms trigger activation of 5'-triphosphorylated 2'-5'oligoadenylate synthetase (OAS) proteins which bind double-stranded RNA and catalyze the synthesis of 5'-triphosphorylated 2'-5' oligoadenylates from ATP (Kristiansen et al. 2011). The p59 protein encoded by the OAS-like (OASL) gene is an atypical member of the OAS family in the sense that it lacks the characteristic 2'-5' oligoadenylate synthetase activity (Hartmann et al. 1998; Rebouillat et al. 1998). Furthermore, OASL contains two tandem ubiquitin-like domains (UBL) in the C-terminus, which are absent in other OAS proteins (Hartmann et al. 1998; Rebouillat et al. 1998). OASL is rapidly induced by virus infection via interferon regulatory factor 3 (IRF3) as well as by IFN signaling and has been shown to have antiviral activities, which requires the UBL domain (Melchjorsen et al. 2009; Sarkar and Sen 2004; Marques et al. 2008; Schoggins et al. 2011). OASL is thought to interact with and enhance RIG1 (DDX58) signaling through its C-terminal ubiquitin-like domain (UBL) by mimicking polyubiquitin (Zhu J et al. 2014). Loss of OASL expression reduced DDX58 signaling and enhanced virus replication in human cells. Conversely, OASL expression suppressed replication of a number of viruses in a DDX58-dependent manner and enhanced DDX58-mediated IFN induction (Zhu J et al. 2014).

Literature references

Zhu, J., Zhang, Y., Ghosh, A., Cuevas, RA., Forero, A., Dhar, J. et al. (2014). Antiviral activity of human OASL protein is mediated by enhancing signaling of the RIG-I RNA sensor. *Immunity, 40*, 936-48. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

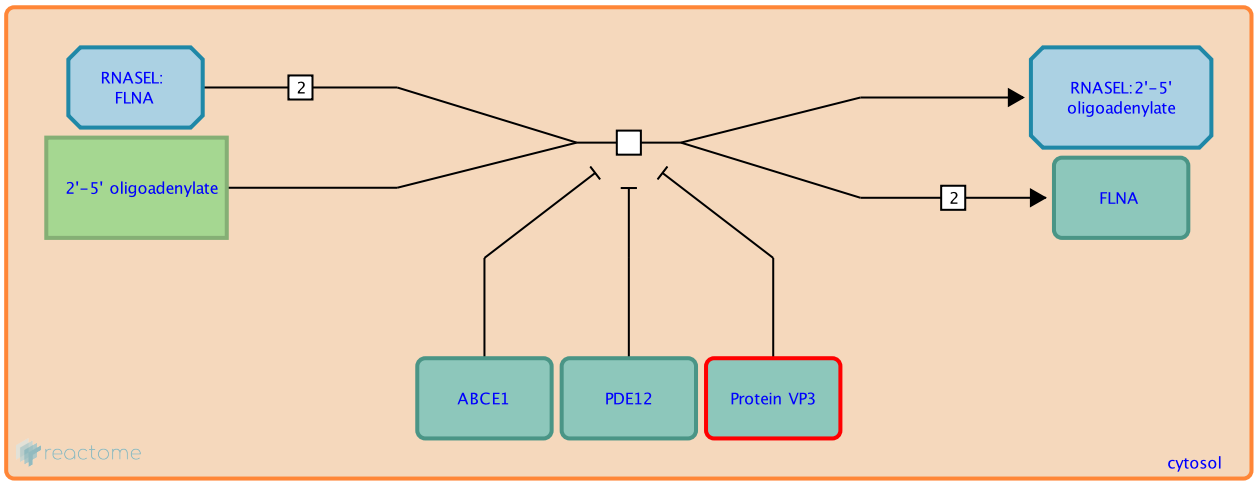
RNASEL binds 2'-5' oligoadenylate ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8985123

Type: transition

Compartments: cytosol



Ribonuclease L (RNASEL) gene encodes an ankyrin (ANK) repeat domain containing dual endoribonuclease-pseudokinase RNase L that functions in the interferon (IFN) antiviral response (Wreschner DH et al. 1982; Zhou A et al.1993; Hassel BA et al. 1993; Huang H et al. 2014; Han Y et al. 2014). Upon activation by viral double-stranded RNA, 5'-triphosphorylated 2'-5'-linked oligoadenylates (2-5A) are synthesized by one of several 2'-5' oligoadenylate synthetases (OAS). The 2-5A binds to monomeric, inactive RNase L causing it to dimerize through the ANK domains (Dong B & Silverman RH 1995; Tanaka N et al. 2004, 2005; Han Y et al., 2012). Activated RNase L cleaves single-stranded viral and cellular RNA, predominantly after UpU and UpA dinucleotides (Floyd-Smith G et al. 1981; Wreschner DH et al. 1981). The triadenylate form of 2-5A is the minimal active molecule, however, longer 2',5'-oligoadenylates retain the ability to activate RNase L (Dong B et al. 1994).

RNase L possesses nine ankyrin repeats (the 9th being incomplete) in the N-terminus, and pseudokinase and nuclease domains in the C-terminus, which is also termed the kinase-extension nuclease (KEN) domain (Hassel BA et al. 1993; Tanaka N et al. 2004; Han Y et al. 2014; Huang H et al. 2014). The monomeric RNase L lacks nucleolytic activity, however, deletion of ankyrin repeats caused constitutive, albeit reduced, ribonuclease activity (Dong B et al. 1997). Crystal structure data indicate that 2-5A binds to the second and fourth ankyrin repeats and the pseudokinase domain (Tanaka N et al. 2004; Huang H et al. 2014; Han Y et al. 2014). These interactions, in conjunction with binding between the pseudokinase domains of the two protomers, mediate dimerization and enzymatic activation within minutes (Huang H et al. 2014; Han Y et al. 2012, 2014). Once active, RNase L cleaves ssRNA, including cellular mRNA and rRNA as well as microbial RNAs. In uninfected cells RNase L interacts with the actin-binding protein filamin A (FLNA) to modulate the actin cytoskeleton and inhibit virus entry into cells (Malathi K et al. 2014; Ezelle HJ et al. 2016). Upon infection and activation of its enzymatic activity by 2-5A, RNase L dissociates from FLNA to mediate its antiviral signaling (Malathi K et al. 2014; Ezelle HJ et al. 2016).

Preceded by: OAS1 produces oligoadenylates, OAS2 produces oligoadenylates, OAS3 produces oligoadenylates

Followed by: RNASEL cleaves viral ssRNA, RNASEL cleaves cellular ssRNA

Literature references

Han, Y., Donovan, J., Rath, S., Whitney, G., Chitrakar, A., Korennykh, A. (2014). Structure of human RNase L reveals the basis for regulated RNA decay in the IFN response. *Science, 343*, 1244-8. ↗

Han, Y., Whitney, G., Donovan, J., Korennykh, A. (2012). Innate immune messenger 2-5A tethers human RNase L into active high-order complexes. *Cell Rep, 2*, 902-13. ↗

Malathi, K., Siddiqui, MA., Dayal, S., Naji, M., Ezelle, HJ., Zeng, C. et al. (2014). RNase L interacts with Filamin A to regulate actin dynamics and barrier function for viral entry. *MBio, 5*, e02012. ↗

Ezelle, HJ., Malathi, K., Hassel, BA. (2016). The Roles of RNase-L in Antimicrobial Immunity and the Cytoskeleton-Associated Innate Response. *Int J Mol Sci, 17*. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

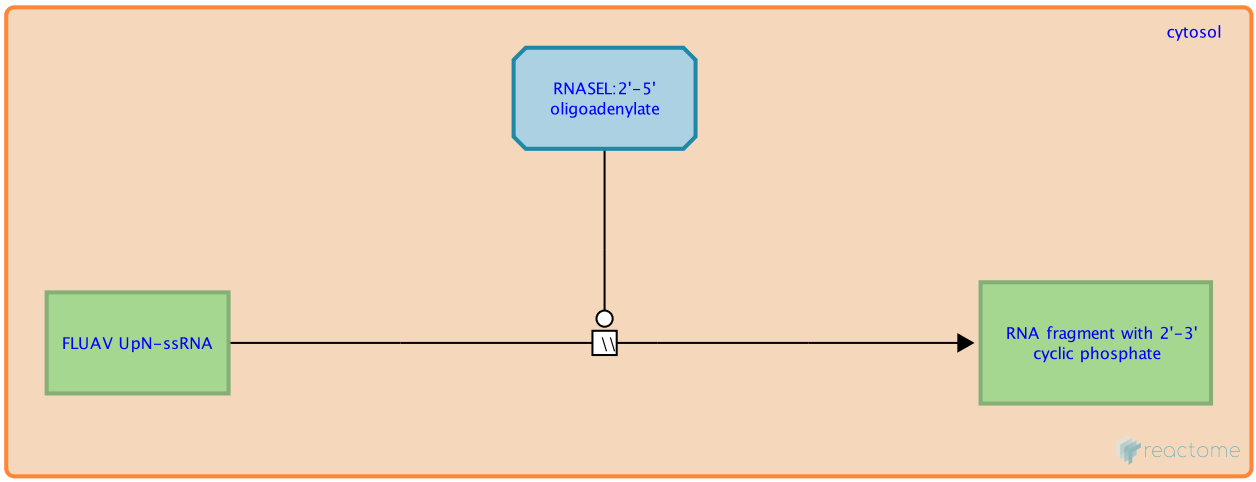
RNASEL cleaves viral ssRNA ↗

Location: OAS antiviral response

Stable identifier: R-HSA-9009941

Type: omitted

Compartments: cytosol



Ribonuclease L (RNase L) is an ankyrin (ANK) repeat domain containing dual endoribonuclease-pseudokinase which is encoded by RNASEL gene (Wreschner DH et al. 1982; Zhou A et al.1993; Hassel BA et al. 1993; Huang H et al. 2014; Han Y et al. 2014). Activated RNase L forms a homodimer (Dong B & Silverman RH 1995) which cleaves within single-stranded regions of different RNA substrates, predominantly after UpAp and UpUp dinucleotides, leaving 2',3'-cyclic phosphoryl and 5'-hydroxyl groups at the termini of the RNA cleavage products (Wreschner DH et al. 1981; Floyd-Smith G et al. 1981; Han Y et al. 2012; Cooper DA et al. 2014). The antiviral effect of RNase L occurs through a combination of effects and depends on the virus and cell type. This includes cleavage of viral genomic ssRNA that prevents viral replication (Cooper DA et al. 2015), cleavage of viral mRNA that inhibits viral protein synthesis, and cleavage of cellular RNA such as mRNA and rRNA that is required for viral replication (Wreschner DH et al. 1981; Silverman RH et al.1983; Brennan-Laun SE et al. 2014; Cooper DA et al. 2014). RNase L induces apoptosis to eliminate virus-infected cells and autophagy to limit viral infections in some circumstances (Zhou A et al. 1997; Castelli JC et al. 1997; Chakrabarti A et al. 2012). Depending on the cell type and basal levels of RNase L, viral and cellular RNA cleavage products induce signaling to the IFN beta gene through RIG-I and/or MDA5 and MAVS (Malathi K et al. 2007; Banerjee S et al. 2014).

Preceded by: RNASEL binds 2'-5' oligoadenylate

Literature references

Cooper, DA., Banerjee, S., Chakrabarti, A., García-Sastre, A., Hesselberth, JR., Silverman, RH. et al. (2015). RNase L targets distinct sites in influenza A virus RNAs. *J. Virol., 89*, 2764-76. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

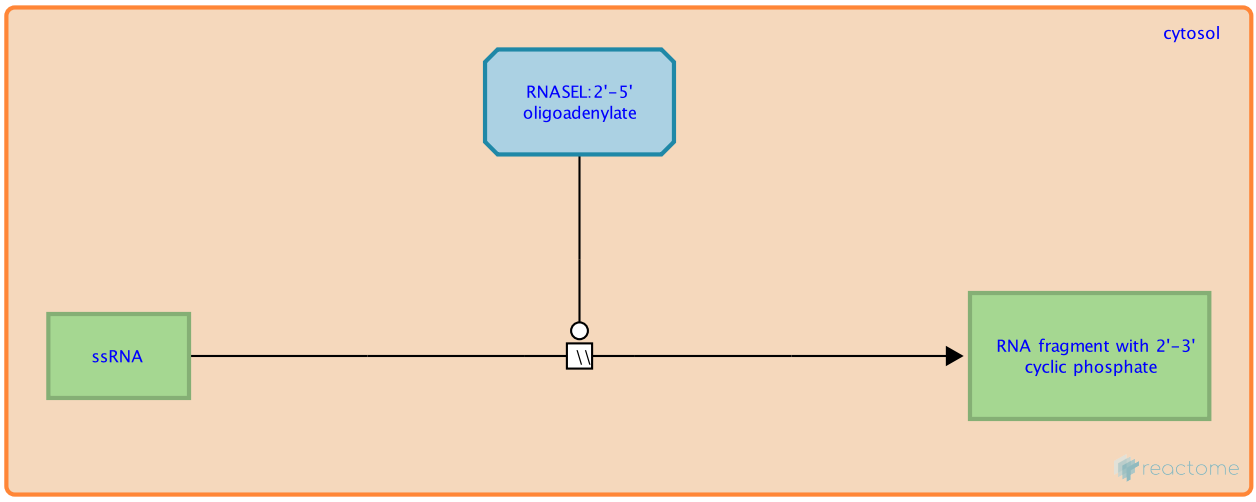
RNASEL cleaves cellular ssRNA ↗

Location: OAS antiviral response

Stable identifier: R-HSA-9009936

Type: omitted

Compartments: cytosol



Ribonuclease L (RNase L) is an ankyrin (ANK) repeat domain containing dual endoribonuclease-pseudokinase which is encoded by RNASEL gene (Wreschner DH et al. 1982; Zhou A et al.1993; Hassel BA et al. 1993; Huang H et al. 2014; Han Y et al. 2014). Activated RNase L forms a homodimer (Dong B & Silverman RH 1995) which cleaves within single-stranded regions of different RNA substrates, predominantly after UpAp and UpUp dinucleotides, leaving 2',3'-cyclic phosphoryl and 5'-hydroxyl groups at the termini of the RNA cleavage products (Wreschner DH et al. 1981; Floyd-Smith G et al. 1981; Han Y et al. 2012; Cooper DA et al. 2014). The antiviral function of RNase L extends beyond direct cleavage of viral RNA and includes also cleavage of cellular RNA such as mRNA and rRNA that is required for viral replication (Wreschner DH et al. 1981; Silverman RH et al.1983; Brennan-Laun SE et al. 2014; Cooper DA et al. 2014). RNase L induces apoptosis to eliminate virus-infected cells and autophagy to limit viral infections in some circumstances (Zhou A et al. 1997; Castelli JC et al. 1997; Chakrabarti A et al. 2012). Depending on the cell type and basal levels of RNase L, viral and cellular RNA cleavage products induce signaling to the IFN beta gene through RIG-I and/or MDA5 and MAVS (Malathi K et al. 2007; Banerjee S etl al. 2014).

Preceded by: RNASEL binds 2'-5' oligoadenylate

Literature references

Cooper, DA., Jha, BK., Silverman, RH., Hesselberth, JR., Barton, DJ. (2014). Ribonuclease L and metal-ion-independent endoribonuclease cleavage sites in host and viral RNAs. *Nucleic Acids Res., 42*, 5202-16. ↗

Silverman, RH., Skehel, JJ., James, TC., Wreschner, DH., Kerr, IM. (1983). rRNA cleavage as an index of ppp(A2'p)nA activity in interferon-treated encephalomyocarditis virus-infected cells. *J. Virol., 46*, 1051-5. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

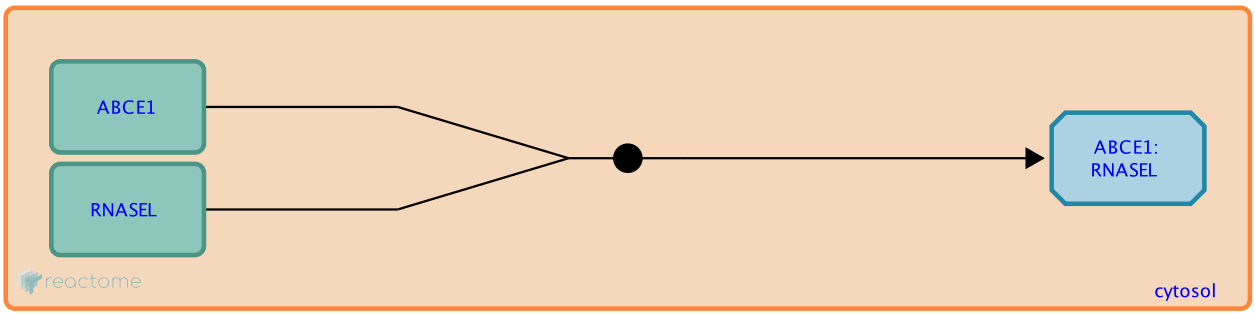
ABCE1 binds RNASEL ↗

Location: OAS antiviral response

Stable identifier: R-HSA-8985201

Type: binding

Compartments: cytosol



ATP-binding cassette sub-family E member 1 (ABCE1, aka RNase L inhibitor, RLI) is a member of the ATP-binding cassette transporters which express in the cytoplasm and the nuclear membrane. ABCE1 is induced during viral infections (Bisbal C et al. 1995; Martinand C et al. 1998, 1999). ABCE1 (RLI) was shown to associate with RNase L inhibiting the endoribonuclease activity of RNase L, thus antagonising the anti-viral effect of the IFN-regulated 2'-5' oligoadenylate/RNase L pathway (Bisbal C et al. 1995; Martinand C et al. 1998, 1999). Furthermore, overexpression or knockdown of ABCE1 (RLI) has inhibitory or promoting effects on the binding of RNase L to 2'-5' oligoadenylates, rRNA cleavage, destabilization of mitochondrial mRNA, antiviral activity, and antitumor activity (Martinand C et al. 1998, 1999; Le Roy F et al. 2001; Malathi K et al. 2004; Huang B et al. 2014; Tian Y et al. 2016). Aside from its role as an RNase-L inhibitor, ABCE1 is believed to be involved in translation termination and ribosome recycling (Dong J et al. 2004; Chen ZQ et al. 2006; Khoshnevis S et al. 2010).

Literature references

Bisbal, C., Martinand, C., Silhol, M., Lebleu, B., Salehzada, T. (1995). Cloning and characterization of a RNAse L inhibitor. A new component of the interferon-regulated 2-5A pathway. *J. Biol. Chem., 270*, 13308-17. ↗

Martinand, C., Montavon, C., Salehzada, T., Silhol, M., Lebleu, B., Bisbal, 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. ↗

Bisbal, C., Salehzada, T., Silhol, M., Martinand, C., Le Roy, F., Lebleu, B. (2001). The 2-5A/RNase L pathway and inhibition by RNase L inhibitor (RLI). *Methods Mol. Biol., 160*, 183-98. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

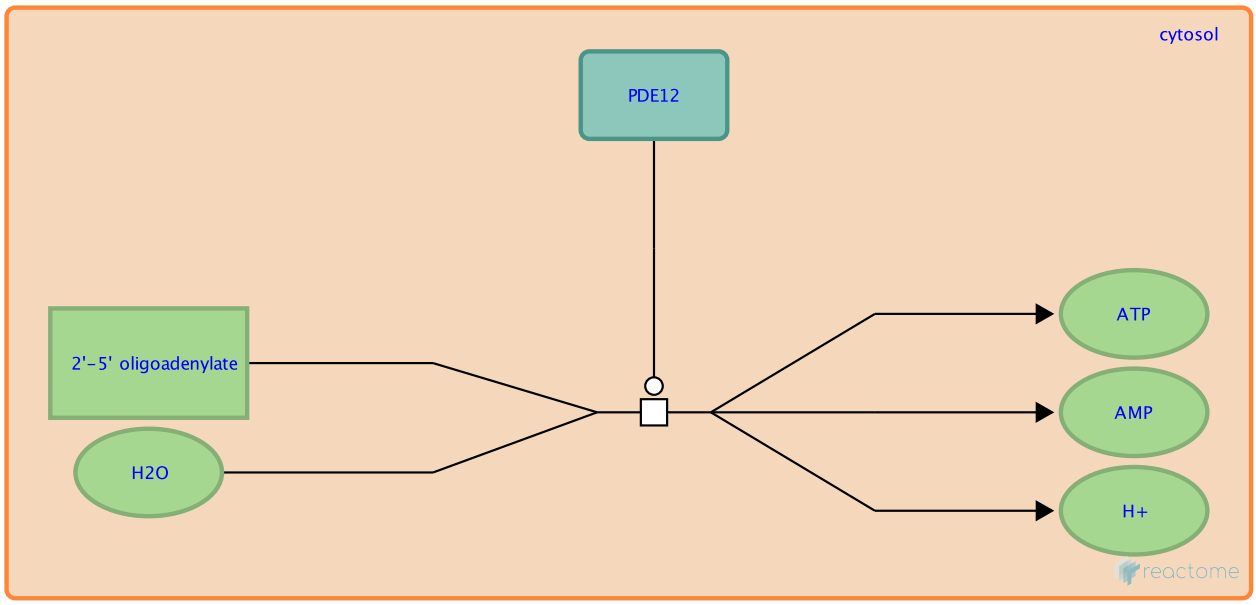
PDE12 cleaves 2'-5' oligoadenylates ↗

Location: OAS antiviral response

Stable identifier: R-HSA-9009950

Type: transition

Compartments: cytosol



Viral infection produces dsRNA that activates OAS isozymes to synthesize 5'-triphosphorylated 2'-5'-linked oligoadenylate (2-5A). Latent ribonuclease L (RNase L) binds 2-5A and oligomerizes into an active complex capable of cleaving ssRNA into retinoic acid-inducible gene-I (RIG-I) and nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3 (NLRP3) inflammasome-activating small RNAs (Malathi K et al. 2007; Chakrabarti A et al. 2015). Activation of RNase L can be attenuated by 2'-phosphodiesterase (PDE12)- mediated degradation of 2-5A. PDE12 is an endonuclease/exonuclease/phosphatase family member of deadenylases with both 3',5'- and 2',5'-phosphodiesterase activities. PDE12 localizes to the mitochondrial matrix and, in addition to degrading 2-5A, removes poly(A) tails from some mitochondrial mRNAs (Kubota K et al. 2004; Poulsen JB et al. 2011; Rorbach J et al. 2011; Silverman RH & Weiss SR 2014; Wood ER et al. 2015). The 2H phosphoesterase, AKAP7, is an unrelated nuclear enzyme that also degrades 2-5A (Gusho E et al. 2014). Several viruses, including some coronaviruses and rotaviruses, encode structurally related 2H phosphoesterases (each with two conserved histidine motifs) that degrade 2-5A and antagonize RNase L mediated antiviral activity (Zhao L et al. 2012; Zhang R et al. 2013; Silverman RH & Weiss SR 2014; Ogden KM et al. 2015; Sui B et al. 2016; Thornbrough JM et al. 2016; Goldstein SA et al. 2017).

Literature references

Kubota, K., Nakahara, K., Ohtsuka, T., Yoshida, S., Kawaguchi, J., Fujita, Y. et al. (2004). Identification of 2'-phosphodiesterase, which plays a role in the 2-5A system regulated by interferon. *J. Biol. Chem., 279*, 37832-41. ↗

Wood, ER., Bledsoe, R., Chai, J., Daka, P., Deng, H., Ding, Y. et al. (2015). The Role of Phosphodiesterase 12 (PDE12) as a Negative Regulator of the Innate Immune Response and the Discovery of Antiviral Inhibitors. *J. Biol. Chem., 290*, 19681-96. ↗

Editions

2017-03-27	Authored	Shamovsky, V.
2017-12-02	Reviewed	D'Eustachio, P.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

Viral 2',5'-PDE cleaves 2'-5' oligoadenylates ↗

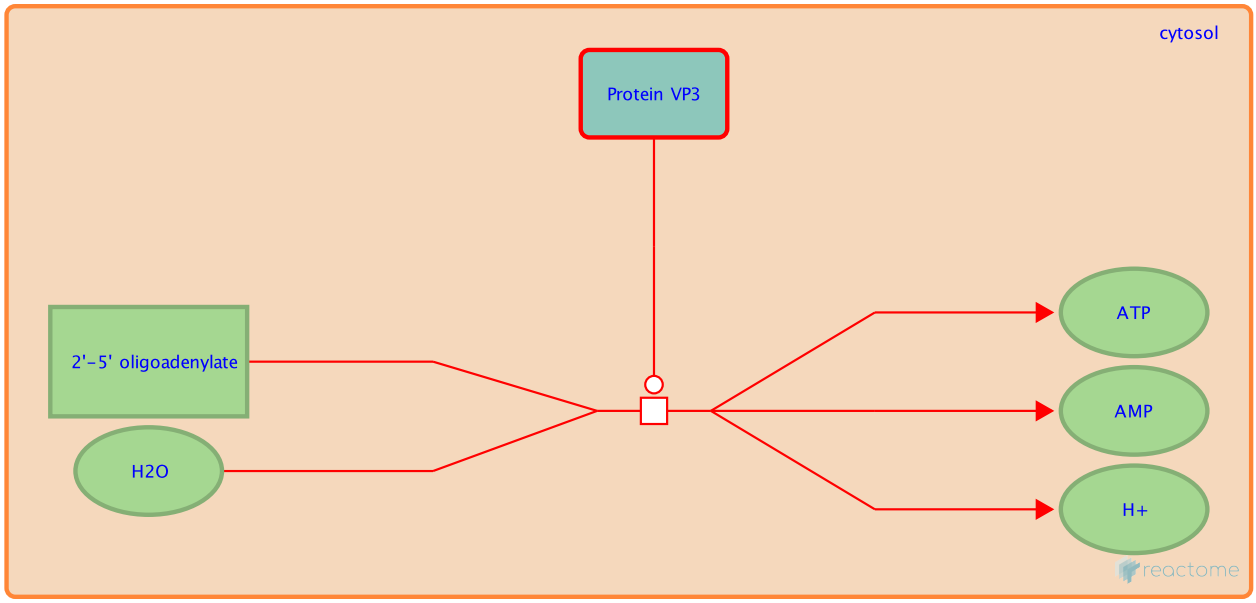
Location: OAS antiviral response

Stable identifier: R-HSA-9615042

Type: transition

Compartments: cytosol

Diseases: viral infectious disease



Viral infection produces dsRNA that activates the 2'-5' oligoadenylate synthetase (OAS) to synthesize 5'-triphosphorylated 2'-5'-linked oligoadenylate from ATP. The 2'-5'-linked oligoadenylate with a chemical structure of ppp5'A(2'p5'A)n contain 2 to greater than 5 adenylyl residues (n>2) and are commonly referred to as 2-5A (Kerr IM & Brown RE 1978). The 2-5As bind latent ribonuclease L (RNase L) which in human is encoded by RNASEL gene. RNase L oligomerizes into an active complex capable of cleaving viral ssRNA and cellular ssRNA to inhibit viral replication and spread (Silverman RH 2007; Malathi K et al. 2007; Chakrabarti A et al. 2015). Viruses have developed diverse strategies to escape the host antiviral effects. Several viruses, including some coronaviruses and rotaviruses, encode structurally related 2H phosphoesterases with two conserved His-x-Ser/Thr motifs in their catalytic sites. The NS4b protein of Middle East respiratory syndrome coronavirus (MERS-CoV), the protein VP3 of rotavirus A (RVA), the non-structural 2 (NS2) protein of human respiratory coronavirus HCoV-OC43 and its homologue ns2 protein of mouse hepatitis virus (MHV) possess enzymatic 2',5-phosphodiesterase (PDE) activity that is capable of antagonizing RNase L and thus countering a potent host antiviral response in mammals (Mazumder R et al., 2002; Zhao L et al. 2012; Zhang R et al. 2013; Silverman RH & Weiss SR 2014; Ogden KM et al. 2015; Sui B et al. 2016; Thornbrough JM et al. 2016; Goldstein SA et al. 2017). The viral 2',5'-PDEs are phylogenetically related to the cellular 2',5'-PDE, a kinase anchoring protein 7 (AKAP7) (Mazumder R et al., 2002; Gold MG et al. 2008; Ogden KM et al. 2015; Brandmann T & Jinek M 2015). Murine AKAP7 was found to cleave the phosphodiester bonds of 2-5A in vitro with rates similar to its viral homologues, ns2 of MHV and VP3 of RVA (Gusho E et al. 2014). Murine AKAP7 (full length and central domain) also effectively degraded 2-5A in intact pIC-transfected human ovarian carcinoma Hey1B cells (Gusho E et al. 2014). The proviral effect of murine AKAP7 required cytoplasmic localization of the PDE domain of AKAP7, whereas full-length AKAP7 was observed only in nuclei. Further studies are needed to identify the subcellular compartment of 2',5'-PDE activity of AKAP7.

The Reactome event shows a cleavage of 2-5A by RVA protein VP3 as an example of viral 2',5'-PDE activity that antagonizes dsRNA signaling to RNase L.

Literature references

Zhang, R., Jha, BK., Ogden, KM., Dong, B., Zhao, L., Elliott, R. et al. (2013). Homologous 2',5'-phosphodiesterases from disparate RNA viruses antagonize antiviral innate immunity. *Proc. Natl. Acad. Sci. U.S.A., 110*, 13114-9. ↗

Silverman, RH., Weiss, SR. (2014). Viral phosphodiesterases that antagonize double-stranded RNA signaling to RNase L by degrading 2-5A. *J. Interferon Cytokine Res., 34*, 455-63. ↗

Editions

2018-07-27	Authored	Shamovsky, V.
2018-07-31	Edited	Shamovsky, V.
2018-07-31	Reviewed	Silverman, RH.

Table of Contents