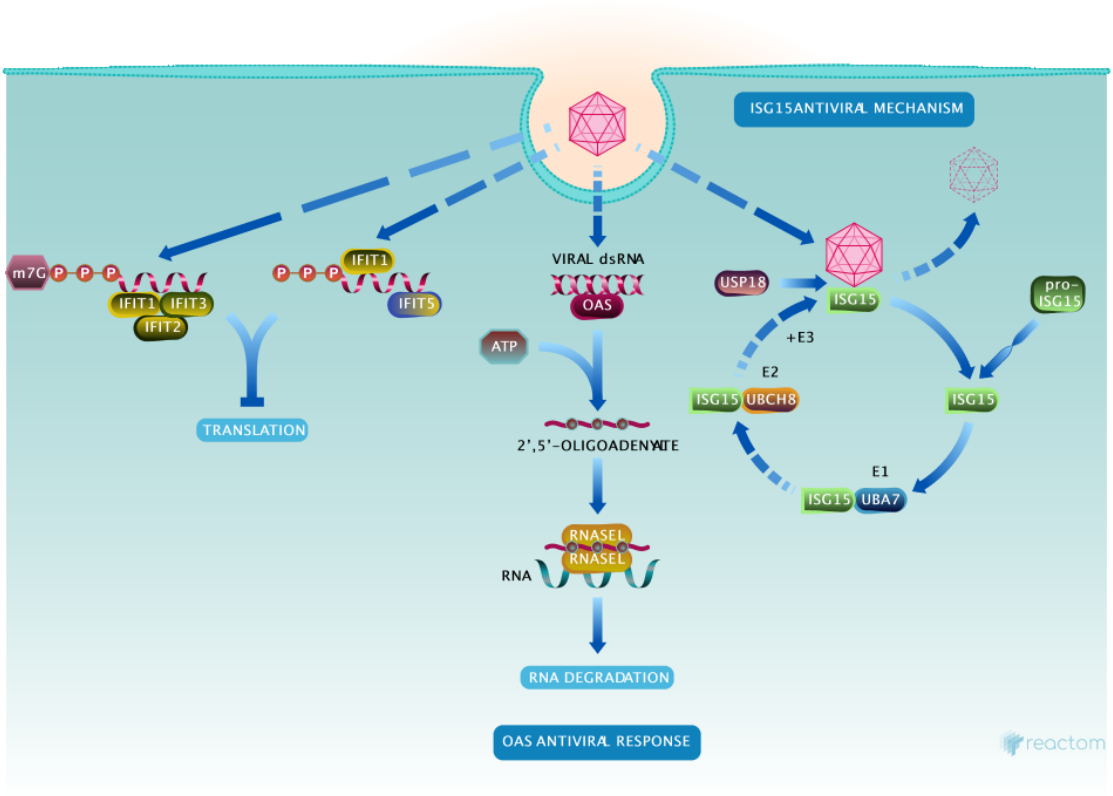
Antiviral mechanism by IFN-stimulated genes



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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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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. ↗

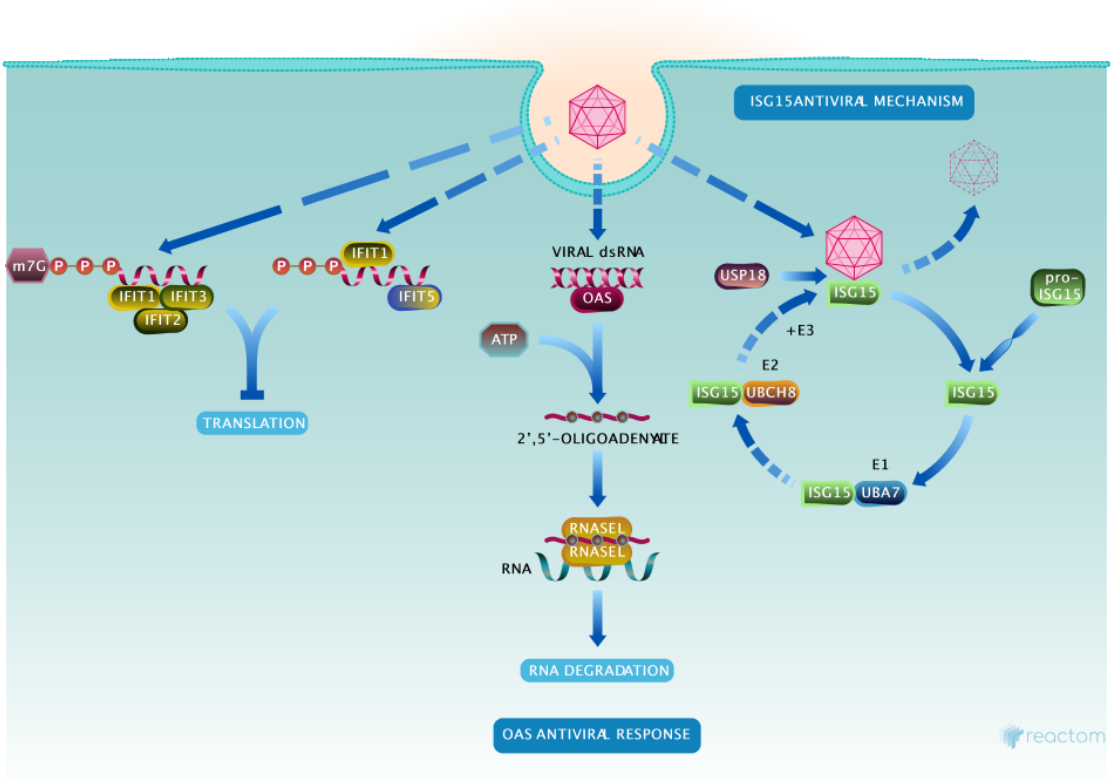
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Antiviral mechanism by IFN-stimulated genes ↗

Stable identifier: R-HSA-1169410

Compartments: cytosol



Interferons activate JAK–STAT signaling, which leads to the transcriptional induction of hundreds of IFN-stimulated genes (ISGs). The ISG-encoded proteins include direct effectors which inhibit viral infection through diverse mechanisms as well as factors that promote adaptive immune responses. The ISG proteins generated by IFN pathways plays key roles in the induction of innate and adaptive immune responses.

Editions

2011-01-18	Authored, Edited	Garapati, P V.
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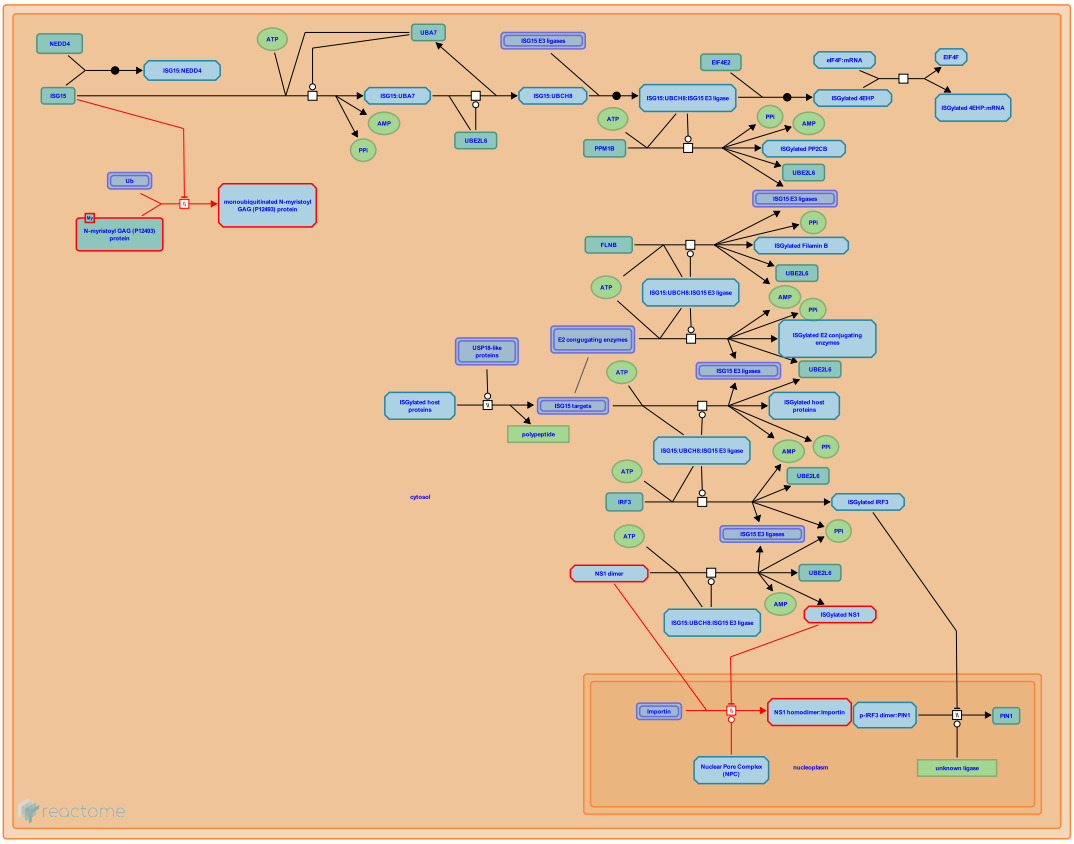
ISG15 antiviral mechanism ↗

Location: Antiviral mechanism by IFN-stimulated genes

Stable identifier: R-HSA-1169408

Compartments: cytosol



Interferon-stimulated gene 15 (ISG15) is a member of the ubiquitin-like (Ubl) family. It is strongly induced upon exposure to type I Interferons (IFNs), viruses, bacterial LPS, and other stresses. Once released the mature ISG15 conjugates with an array of target proteins, a process termed ISGylation. ISGylation utilizes a mechanism similar to ubiquitination, requiring a three-step enzymatic cascade. UBE1L is the ISG15 E1 activating enzyme which specifically activates ISG15 at the expense of ATP. ISG15 is then transfered from E1 to the E2 conjugating enzyme UBCH8 and then to the target protein with the aid of an ISG15 E3 ligase, such as HERC5 and EFP. Hundreds of target proteins for ISGylation have been identified. Several proteins that are part of antiviral signaling pathways, such as RIG-I, MDA5, Mx1, PKR, filamin B, STAT1, IRF3 and JAK1, have been identified as targets for ISGylation. ISG15 also conjugates some viral proteins, inhibiting viral budding and release. ISGylation appears to act either by disrupting the activity of a target protein and/or by altering its localization within the cell.

Literature references

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Zhao, C., Denison, C., Huibregtse, JM., Gygi, S., Krug, RM. (2005). Human ISG15 conjugation targets both IFN-induced and constitutively expressed proteins functioning in diverse cellular pathways. *Proc Natl Acad Sci U S A, 102*, 10200-5. ↗

Editions

2011-01-18	Authored, Edited	Garapati, P V.
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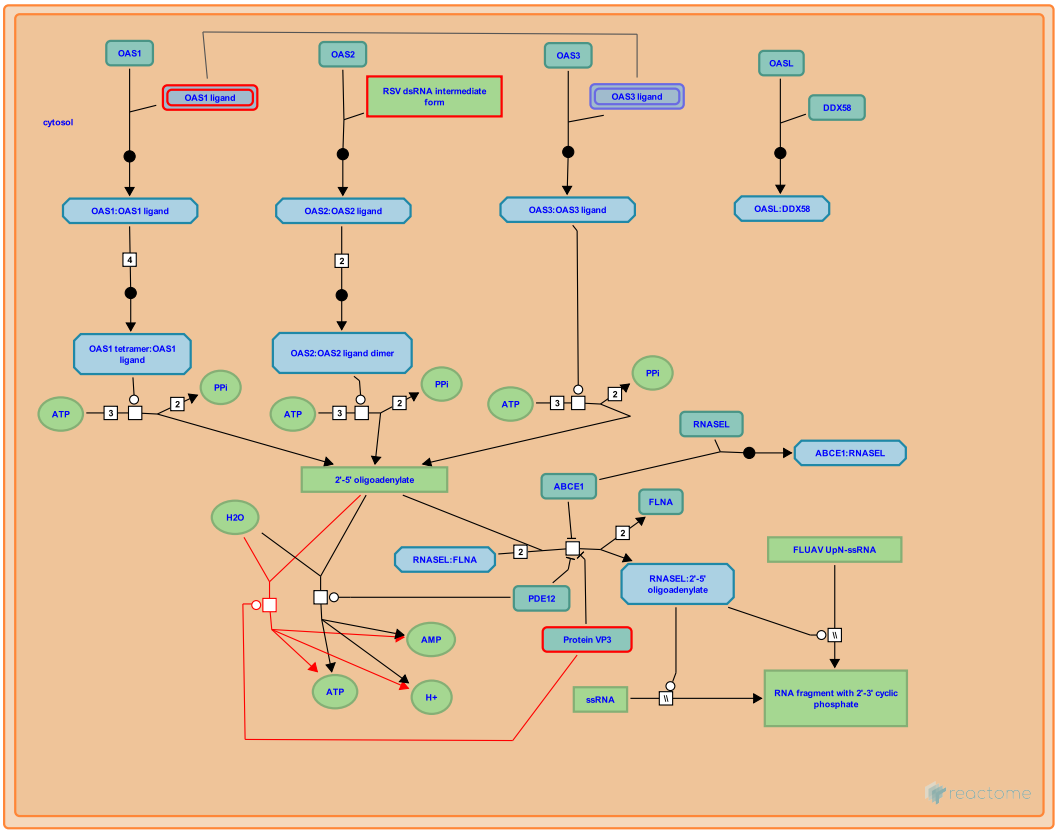
OAS antiviral response ↗

Location: Antiviral mechanism by IFN-stimulated genes

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

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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.

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