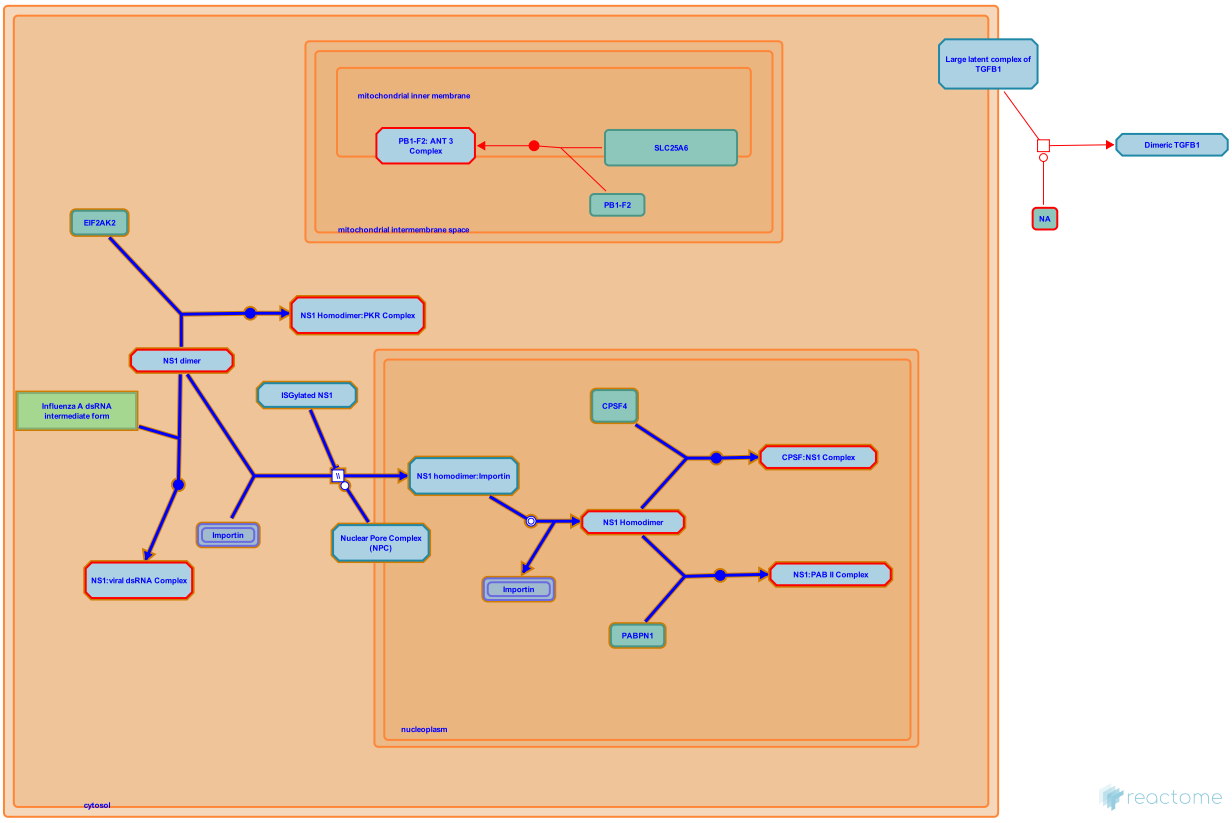
NS1 Mediated Effects on Host Pathways



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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).

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. ↗

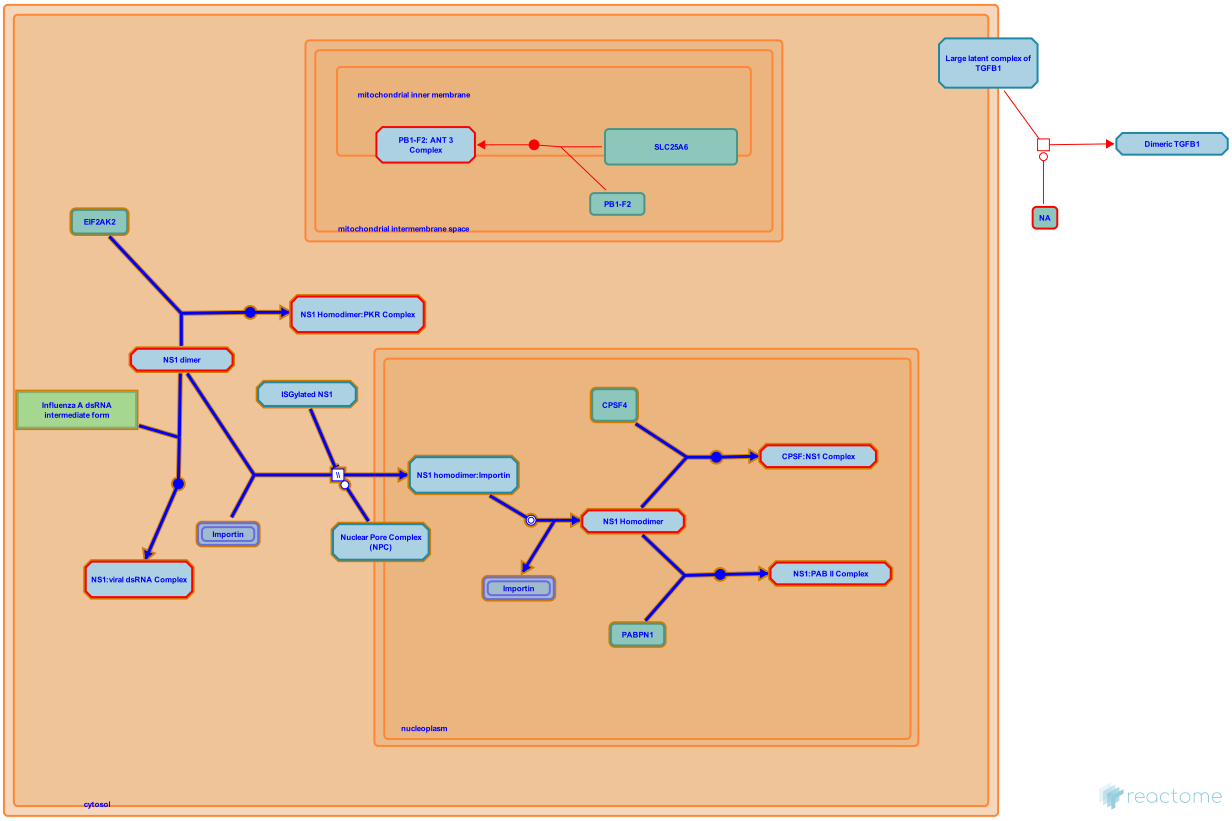
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

NS1 Mediated Effects on Host Pathways ↗

Stable identifier: R-HSA-168276

Diseases: influenza



Viral NS1 protein is a nuclear, dimeric protein that is highly expressed in infected cells and has dsRNA-binding activity. The RNA-binding domain lies within the N-terminal portion of the protein. The NS1 RNA-binding domain forms a symmetric homodimer with a six-helical fold. Mutational analysis has demonstrated that dimer formation is crucial for RNA-binding. The basic residues are believed to make contact with the phosphate backbone of the RNA which is consistent with an observed lack of sequence specificity. Neither NS1 nor its bound RNA undergo any significant structural changes upon binding. The NS1 dimer spans the minor groove of canonical A-form dsRNA. The non-RNA binding portion of NS1 has been termed the effector domain and includes binding sites for host cell poly (A)-binding protein II (PABII) and the 30kDa subunit of cleavage and polyadenylation specificity factor (CPSF).

Literature references

Palese, P., Shaw, ML. (2001). Orthomyxoviridae: The Viruses and Their Replication. *Fields Virology, 5th edition D.M. Knipe and P.M. Howley, Editors. 2006, Lippencott Williams and Wilkins: Philadelphia ISBN-10: 0-7817-6060-7*, 1647-1689. ↗

Editions

2004-05-13	Reviewed	Gale M, Jr.
2013-11-18	Authored, Edited	Gillespie, ME.

Translocation of Influenza A virus nonstructural protein 1 (NS1A) into the nucleus ↗

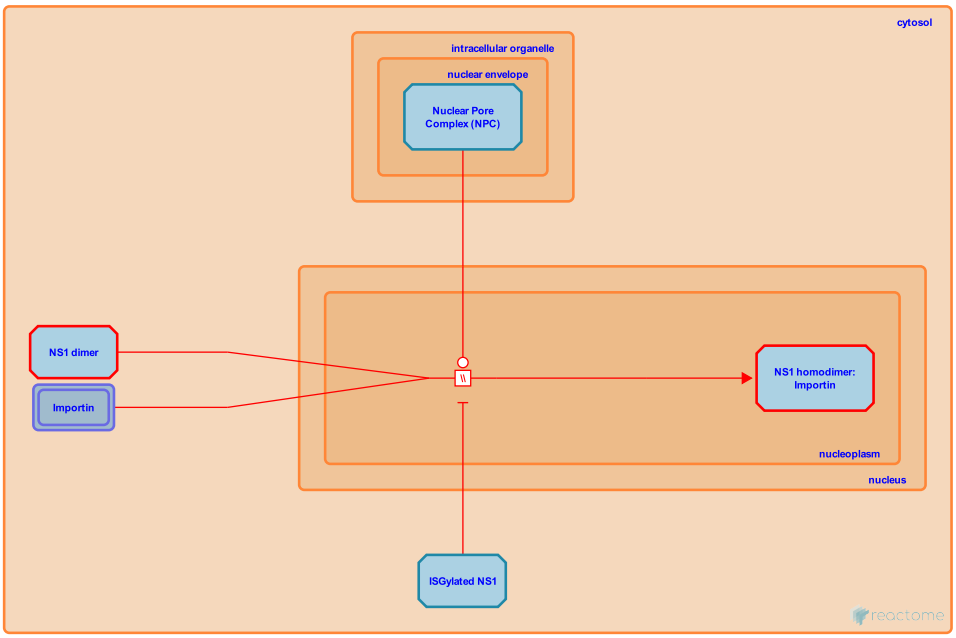
Location: NS1 Mediated Effects on Host Pathways

Stable identifier: R-HSA-1176059

Type: omitted

Compartments: nucleoplasm, cytosol

Diseases: influenza



Influenza A virus nonstructural protein 1 (NS1A) is a multifunctional protein that exists as a dimer and is involved in the inhibition of host cell antiviral pre-mRNA processing and counteracts host cell antiviral responses. Unlike most other RNA viruses, influenza viruses replicate in the nucleus of the host cells. NS1A protein carries two nuclear localization signal (NLS) elements and these sequence elements are recognized by importin-alpha/beta. In the cytoplasm NS1A binds to importin-alpha/beta and these protein complexes are then translocated into the nucleus through the nuclear pore complex (NPC).

Note:Reactions directly involving interactions of human host proteins with foreign ones are highlighted in red.

Literature references

O'Neill, RE., Jaskunas, R., Blobel, G., Palese, P., Moroianu, J. (1995). Nuclear import of influenza virus RNA can be mediated by viral nucleoprotein and transport factors required for protein import. *J Biol Chem, 270*, 22701-4. ↗

Cros, JF., Garcia-Sastre, A., Palese, P. (2005). An unconventional NLS is critical for the nuclear import of the influenza A virus nucleoprotein and ribonucleoprotein. *Traffic, 6*, 205-13. ↗

Melén, K., Kinnunen, L., Fagerlund, R., Ikonen, N., Twu, KY., Krug, RM. et al. (2007). Nuclear and nucleolar targeting of influenza A virus NS1 protein: striking differences between different virus subtypes. *J Virol, 81*, 5995-6006. ↗

Editions

2004-05-13	Reviewed	Gale M, Jr.
2013-11-18	Authored, Edited	Gillespie, ME.

Release of NS1 homodimer ↗

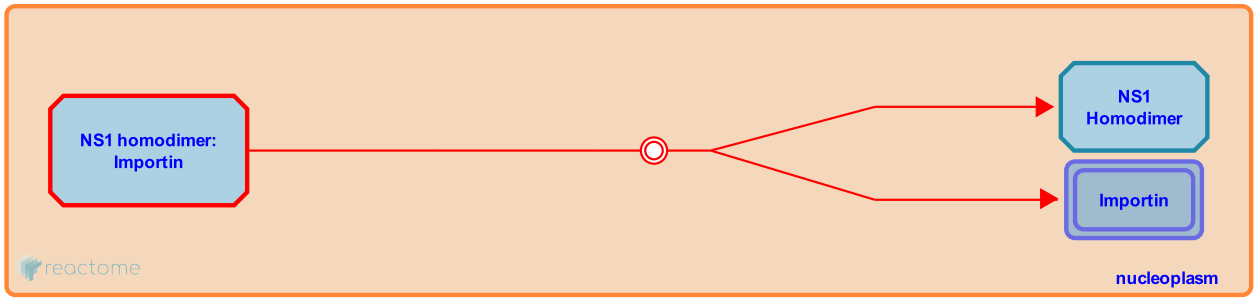
Location: NS1 Mediated Effects on Host Pathways

Stable identifier: R-HSA-6791035

Type: dissociation

Compartments: nucleoplasm

Diseases: influenza



Once the NS1 homodimer is imported into the nucleus, the importin complex releases the NS1 homodimer.

Literature references

Chen, Z., Li, Y., Krug, RM. (1999). Influenza A virus NS1 protein targets poly(A)-binding protein II of the cellular 3'-end processing machinery. *EMBO J, 18*, 2273-83. ↗

Bergmann, M., Garcia-Sastre, A., Carnero, E., Pehamberger, H., Wolff, K., Palese, P. et al. (2000). Influenza virus NS1 protein counteracts PKR-mediated inhibition of replication. *J. Virol., 74*, 6203-6. ↗

Fortes, P., Beloso, A., Ortin, J. (1994). Influenza virus NS1 protein inhibits pre-mRNA splicing and blocks mRNA nucleocytoplasmic transport. *EMBO J, 13*, 704-12. ↗

Nemeroff, ME., Barabino, SM., Li, Y., Keller, W., Krug, RM. (1998). Influenza virus NS1 protein interacts with the cellular 30 kDa subunit of CPSF and inhibits 3'end formation of cellular pre-mRNAs. *Mol Cell, 1*, 991-1000. ↗

Editions

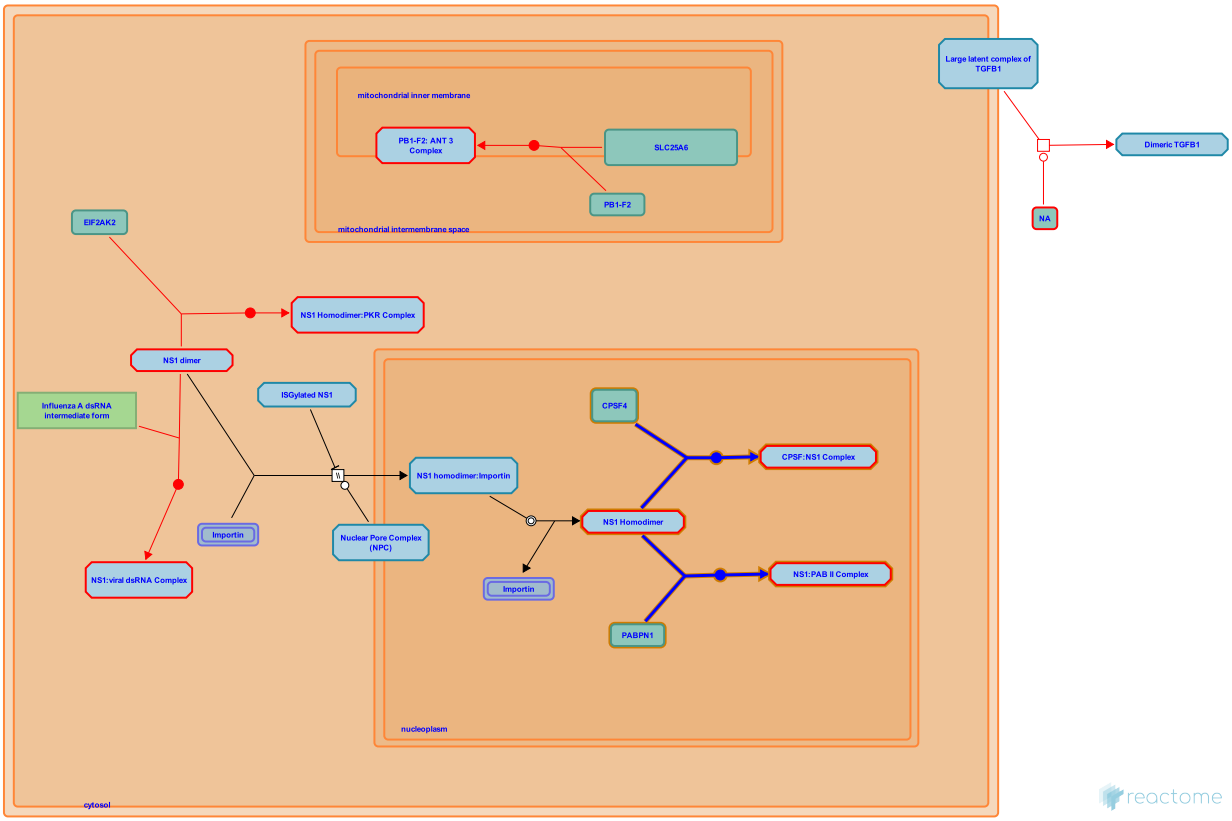
2004-05-13	Reviewed	Gale M, Jr.
2013-11-18	Authored, Edited	Gillespie, ME.

Inhibition of Host mRNA Processing and RNA Silencing ↗

Location: NS1 Mediated Effects on Host Pathways

Stable identifier: R-HSA-168315

Diseases: influenza



The Influenza Virus NS1 protein inhibits the cleavage and polyadenylation specificity factor CPSF and the PABII components of the host cell 3' end processing machinery, preventing efficient 3' end processing of host pre-mRNAs. NS1 also inhibits the splicing of pre-mRNAs, resulting in their retention within the host cell nucleus.

Literature references

Chen, Z., Li, Y., Krug, RM. (1999). Influenza A virus NS1 protein targets poly(A)-binding protein II of the cellular 3'-end processing machinery. *EMBO J, 18*, 2273-83. ↗

Fortes, P., Beloso, A., Ortin, J. (1994). Influenza virus NS1 protein inhibits pre-mRNA splicing and blocks mRNA nucleocytoplasmic transport. *EMBO J, 13*, 704-12. ↗

Lu, Y., Qian, XY., Krug, RM. (1994). The influenza virus NS1 protein: a novel inhibitor of pre-mRNA splicing. *Genes Dev, 8*, 1817-28. ↗

Editions

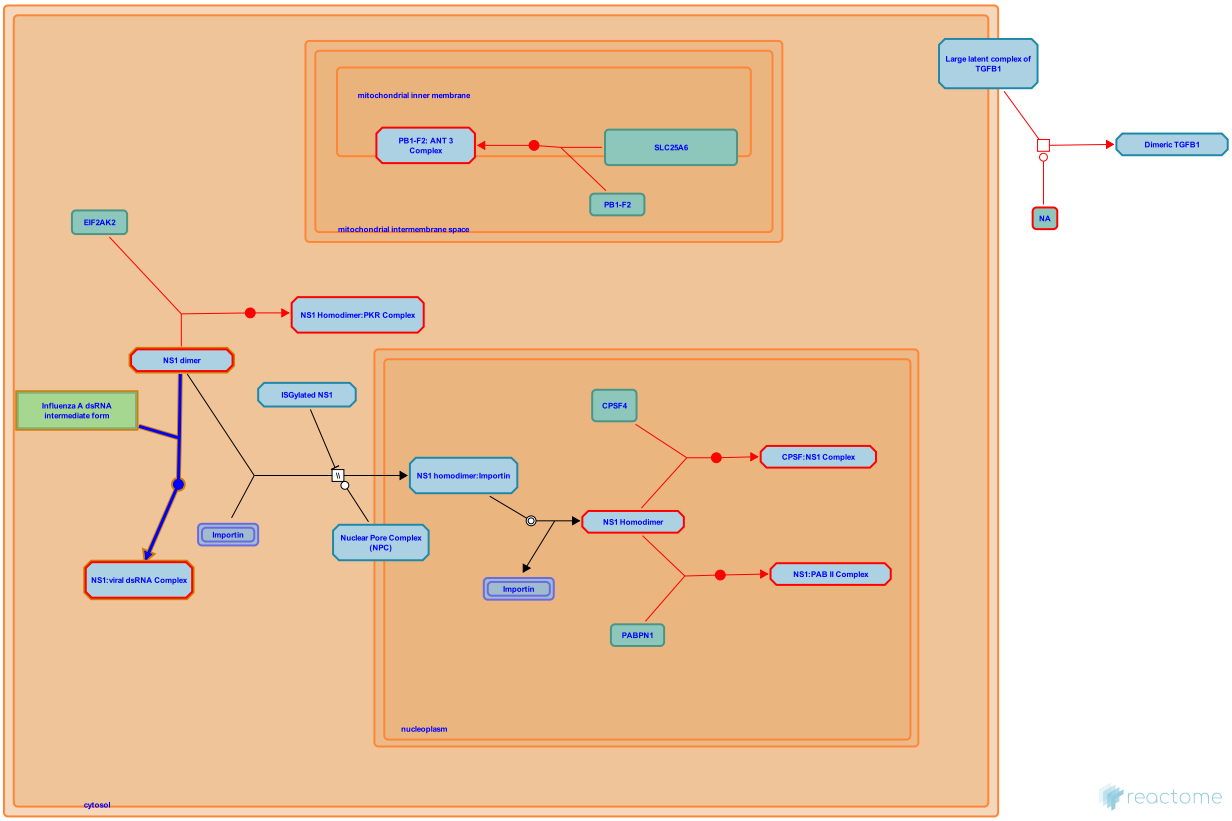
2004-05-13	Reviewed	Gale M, Jr.
2013-11-18	Authored, Edited	Gillespie, ME.

Inhibition of Interferon Synthesis ↗

Location: NS1 Mediated Effects on Host Pathways

Stable identifier: R-HSA-168305

Diseases: influenza



Interferon Synthesis is inhibited.

Editions

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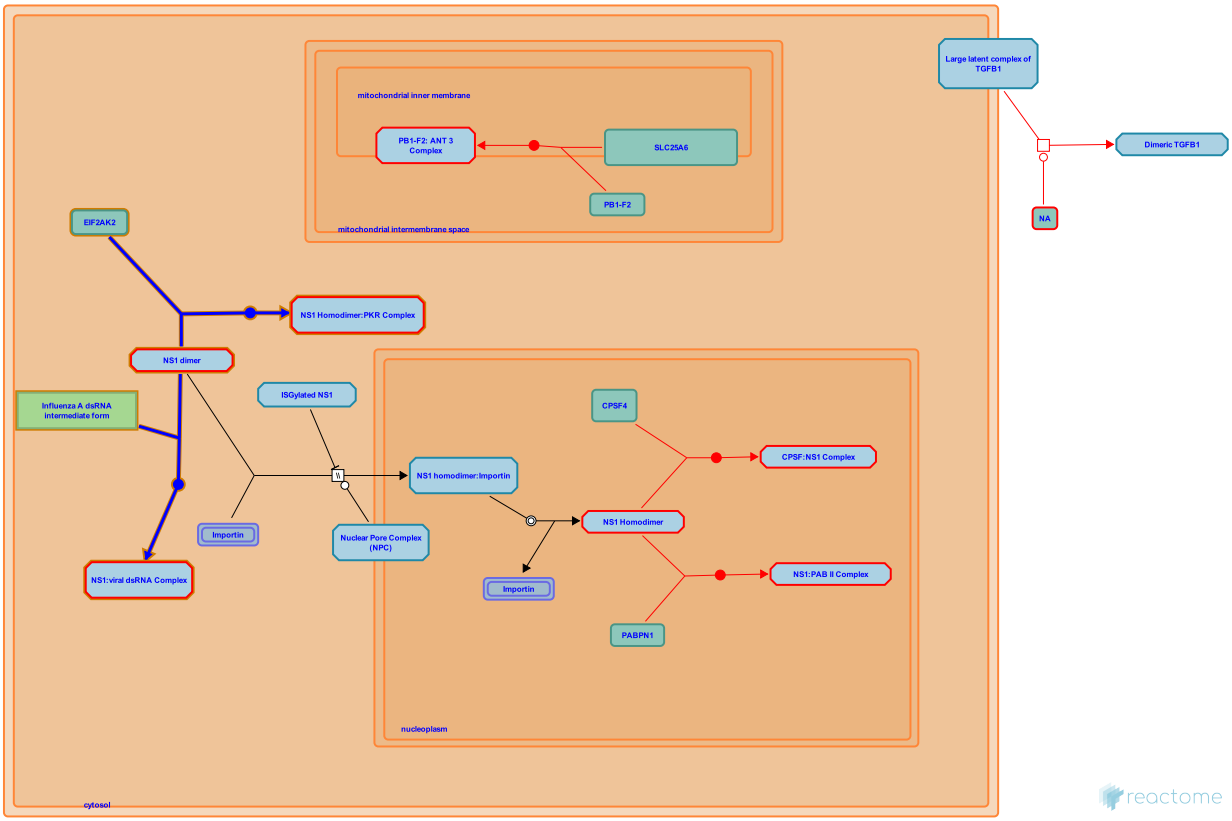
2013-11-18	Authored, Edited	Gillespie, ME.

Inhibition of PKR ↗

Location: NS1 Mediated Effects on Host Pathways

Stable identifier: R-HSA-169131

Diseases: influenza



The key role played by PKR in the innate response to virus infection is emphasized by the large number of viruses that encode PKR inhibitors.

Editions

2004-05-13	Reviewed	Gale M, Jr.
2013-11-18	Authored, Edited	Gillespie, ME.

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