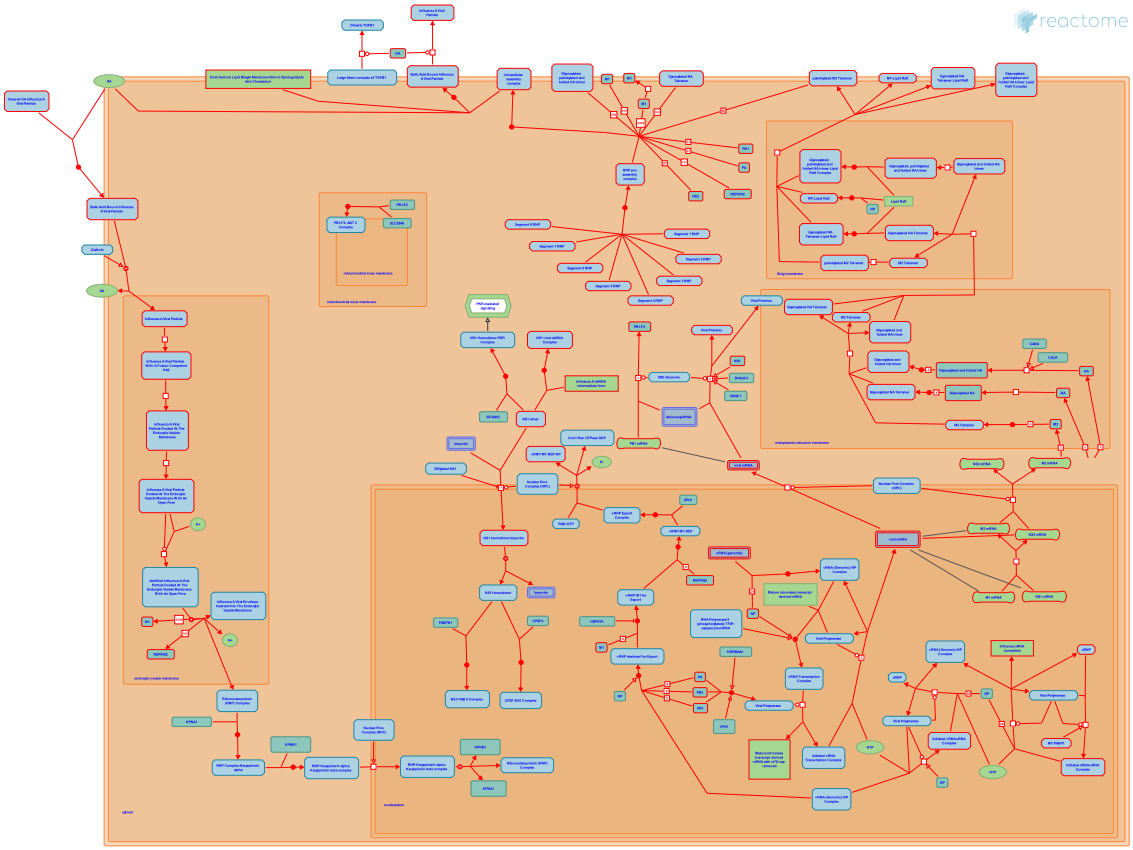
Influenza Infection



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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. ↗

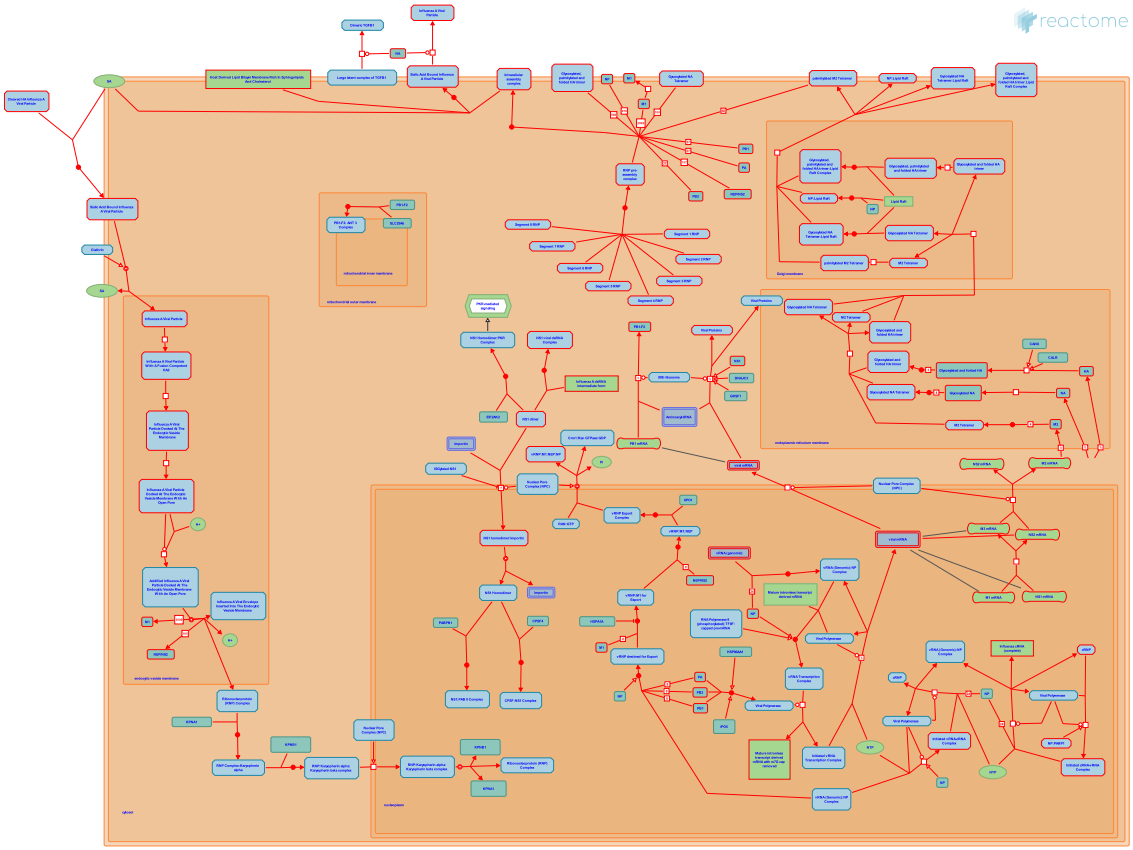
Reactome database release: 88

This document contains 9 pathways and 1 reaction (see Table of Contents)

Influenza Infection ↗

Stable identifier: R-HSA-168255

Diseases: influenza



For centuries influenza epidemics have plagued man; with influenza probably being the disease described by Hippocrates in 412 BC. Today it remains a major cause of morbidity and mortality worldwide with large segments of the human population affected every year. Many animal species can be infected by influenza viruses, often with catastrophic consequences. An influenza pandemic is a continuing global level threat. The 1918 influenza pandemic is a modern example of how devastating such an event could be with an estimated 50 million deaths worldwide.

Influenza viruses belong to the family of Orthomyxoviridae; viruses with segmented RNA genomes that are negative sense and single-stranded (Baltimore 1971). Influenza virus strains are named according to their type (A, B, or C), the species from which the virus was isolated (omitted if human), location of isolate, the number of the isolate, the year of isolation, and in the case of influenza A viruses, the hemagglutinin (H) and neuraminidase (N) subtype. For example, the virus of H5N1 subtype isolated from chickens in Hong Kong in 1997 is: influenza A/chicken/Hong Kong/220/97(H5N1) virus. Currently 16 different hemagglutinin (H1 to H16) subtypes and 9 different neuraminidase (N1 to N9) subtypes are known for influenza A viruses. Most human disease is due to influenza viruses of the A type. The events of influenza infection have been annotated in Reactome primarily use protein and genome references to the Influenza A virus A/Puerto Rico/8/1934 H1N1 strain. The influenza virus particle initially associates with a human host cell by binding to sialic acid receptors on the host cell surface. Sialic acids are found on many vertebrate cells and numerous viruses make use of this ubiquitous receptor. The bound virus is endocytosed by one of four distinct mechanisms. Once endocytosed the low endosomal pH sets in motion a number of steps that lead to viral membrane fusion mediated by the viral hemagglutinin (HA) protein, and the eventual release of the uncoated viral ribonucleoprotein complex into the cytosol of the host cell. The ribonucleoprotein complex is transported through the nuclear pore into the nucleus. Once in the nucleus, the incoming negative-sense viral RNA (vRNA) is transcribed into messenger RNA (mRNA) by a primer-dependent mechanism. Replication occurs via a two step process. A full-length complementary RNA (cRNA), a positive-sense copy of the vRNA, is first made and this in turn is used as a template to produce more vRNA. The viral proteins are expressed and processed and eventually assemble with vRNAs at what will become the budding sites on the host cell membrane. The viral protein and ribonucleoprotein complexes are assembled into complete viral particles and bud from the host cell, enveloped in the host cell's membrane.

Infection of a human host cell with influenza virus triggers an array of defensive host processes. This coevolution

has driven the development of host processes that interfere with viral replication, notably the production of type I interferon. At the some time the virus counters these responses with the viral NS1 protein playing a central role in the viral response to the host cells defense.

Literature references

Shaw, ML., Palese, P. (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

2004-05-12	Reviewed	Garcia-Sastre, A.
2006-01-05	Authored	Luo, F., Squires, B., Scheuermann, RH.
2006-10-31	Reviewed	Garcia-Sastre, A., Squires, B.
2007-05-01	Reviewed	Rush, MG., Squires, B.

Binding of the influenza virion to the host cell ↗

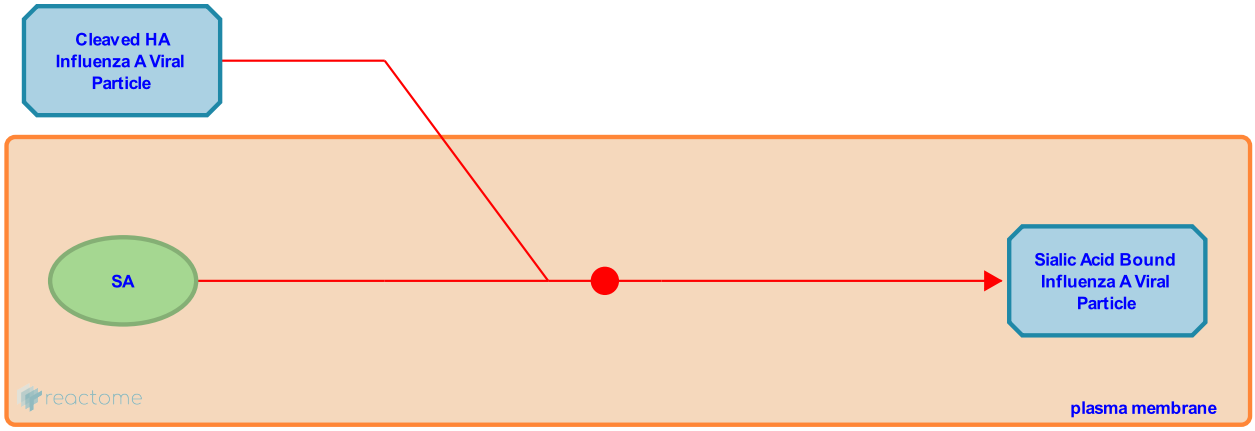
Location: Influenza Infection

Stable identifier: R-HSA-168272

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: influenza



Influenza viruses bind via their surface HA (hemagglutinin) to sialic acid in alpha 2,3 or alpha 2,6 linkage with galactose on the host cell surface. Sialic acid in 2,6 linkages is characteristic of human cells while 2,3 linkages are characteristic of avian cells. The specificity of influenza HA for sialic acid in alpha 2,6 or alpha 2,3 linkages is a feature restricting the transfer of influenza viruses between avian species and humans. This species barrier can be overcome, however. Notably, passaged viruses adapt to their host through mutation in the receptor binding site of the viral HA gene.

Followed by: Entry of Influenza Virion into Host Cell via Endocytosis

Literature references

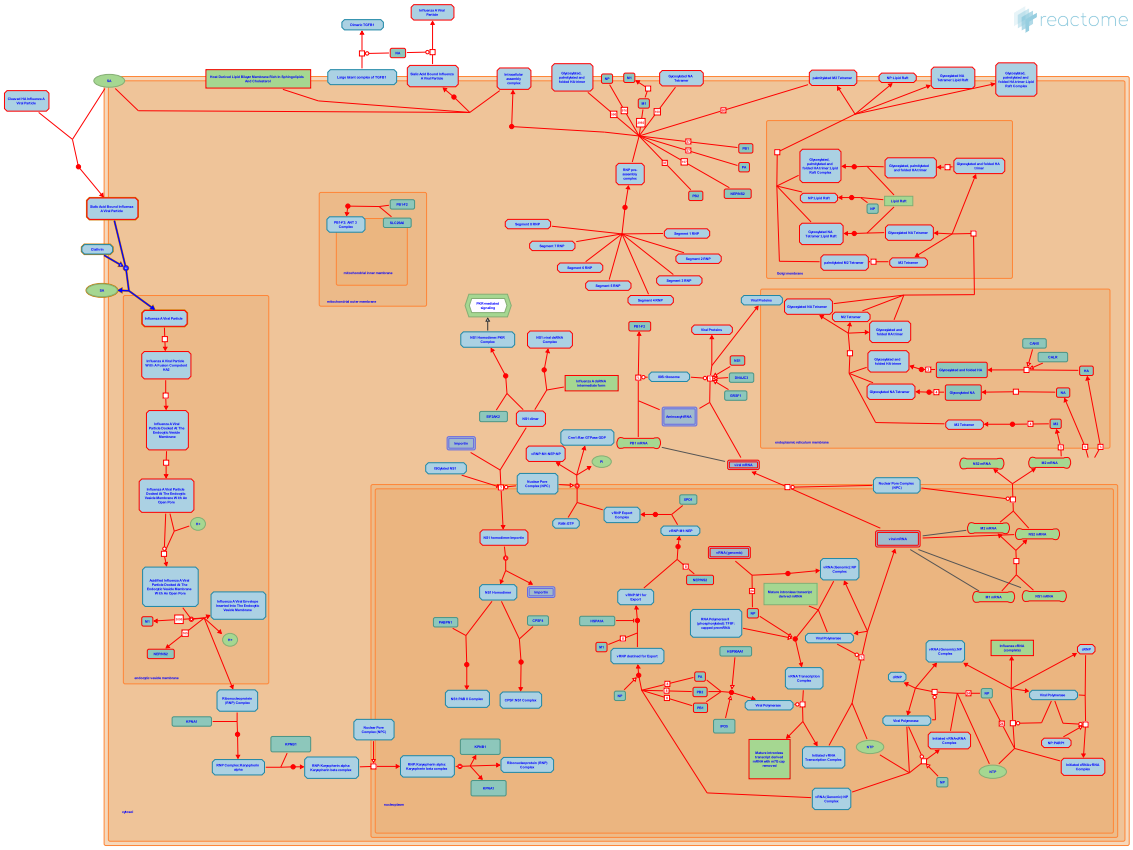
Shaw, ML., Palese, P. (2001). Orthomyxoviridae: The Viruses and Their Replication. *Fields Virology, 5th edition D.M. Knipe and P.M. Howley, Editors. 2006, Lippencott Williams and Wilkins: Philadelphia ISBN-10: 0-7817-6060-7*, 1647-1689. ↗

Entry of Influenza Virion into Host Cell via Endocytosis ↗

Location: Influenza Infection

Stable identifier: R-HSA-168275

Diseases: influenza



Virus particles bound to the cell surface can be internalized by four mechanisms. Most internalization appears to be mediated by clathrin-coated pits, but internalization via caveolae, macropinocytosis, and by non-clathrin, non-caveolae pathways has also been described for influenza viruses.

Literature references

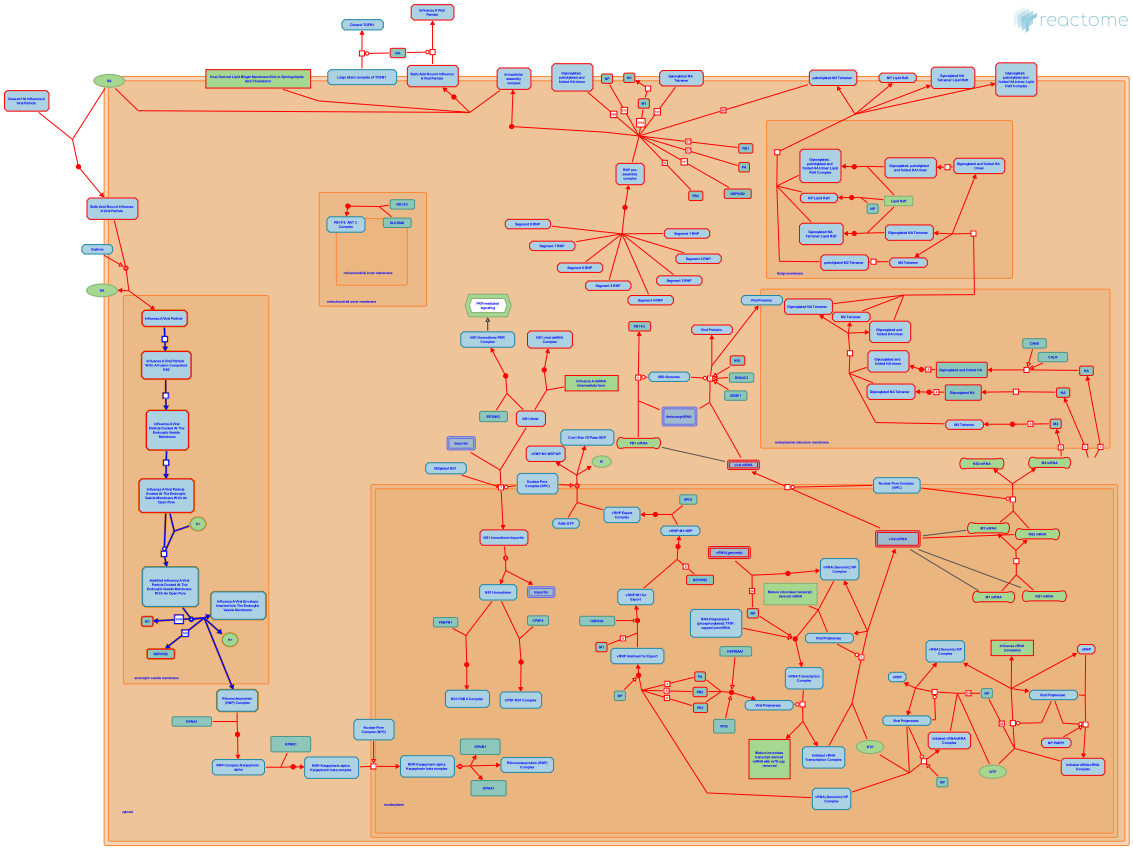
Shaw, ML., Palese, P. (2001). Orthomyxoviridae: The Viruses and Their Replication. *Fields Virology, 5th edition D.M. Knipe and P.M. Howley, Editors. 2006, Lippencott Williams and Wilkins: Philadelphia ISBN-10: 0-7817-6060-7*, 1647-1689. ↗

Fusion and Uncoating of the Influenza Virion ↗

Location: Influenza Infection

Stable identifier: R-HSA-168270

Diseases: influenza



Uncoating of viral particles takes place in the host cell endosome. Acidification of the endosome promotes fusion of the viral and endosomal membranes, causing a structural change in the viral hemagglutinin (HA) and freeing the fusion peptide of its HA2 subunit to interact with the endosome membrane. The concerted structural change of several HA molecules opens up a pore through which the viral RNP passes into the cytosol of the cell. The precise timing and the location of uncoating (early vs. late endosomes) depends on the pH-mediated transition of the specific HA molecule involved. The virus-associated M2 ion channel protein allows the influx of H+ ions into the virion, which disrupts protein-protein interactions, resulting in the release of RNP free of the viral M1 matrix protein. Thus the HA mediated fusion of the viral membrane with the endosomal membrane and the M2-mediated release of the RNP results in the release of the RNP complex into the cytosol. Amantadine and rimantadine have been shown to block the ion channel activity of the M2 protein and thus interfere with uncoating.

Literature references

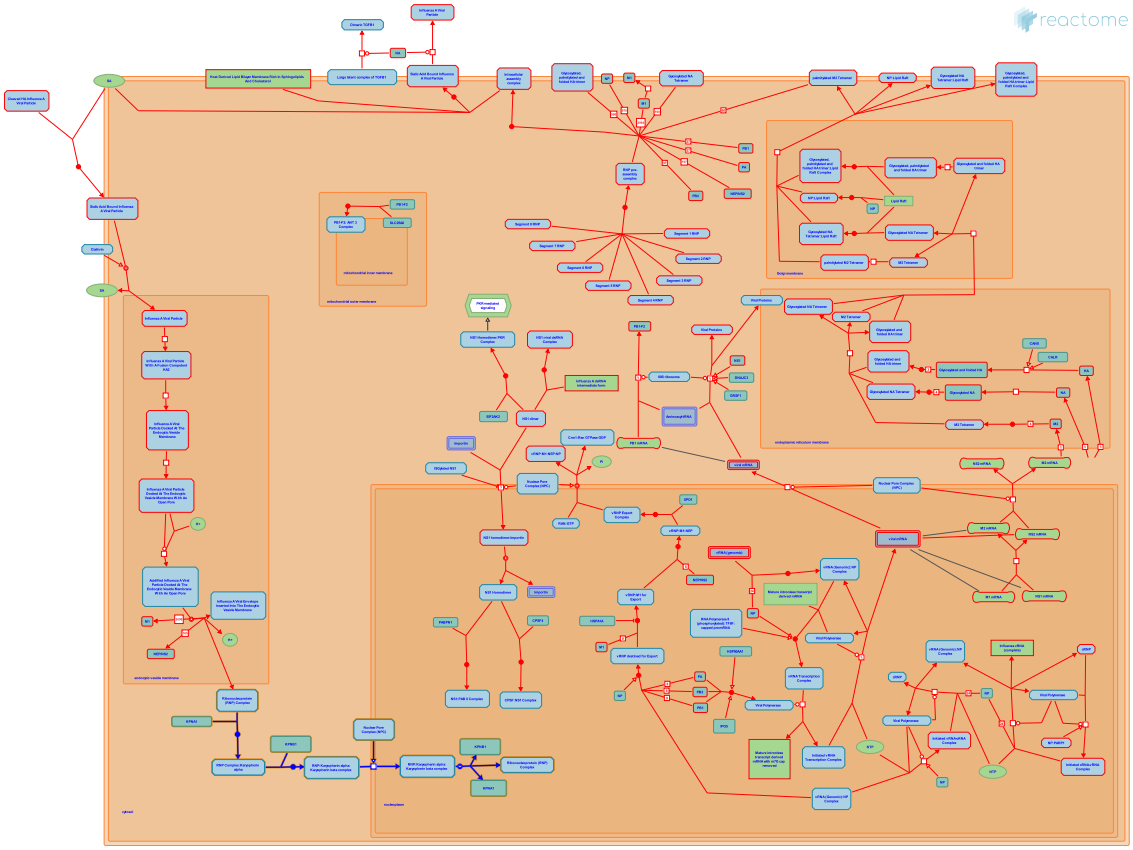
Shaw, ML., Palese, P. (2001). Orthomyxoviridae: The Viruses and Their Replication. *Fields Virology, 5th edition D.M. Knipe and P.M. Howley, Editors. 2006, Lippencott Williams and Wilkins: Philadelphia ISBN-10: 0-7817-6060-7*, 1647-1689. ↗

Transport of Ribonucleoproteins into the Host Nucleus ↗

Location: Influenza Infection

Stable identifier: R-HSA-168271

Diseases: influenza



An unusual characteristic of the influenza virus life cycle is its dependence on the nucleus. Trafficking of the viral genome into and out of the nucleus is a tightly regulated process with all viral RNA synthesis occurring in the nucleus. The eight influenza virus genome segments never exist as naked RNA but are associated with four viral proteins to form viral ribonucleoprotein complexes (vRNPs). The major viral protein in the RNP complex is the nucleocapsid protein (NP), which coats the RNA. The remaining proteins PB1, PB2 and PA bind to the partially complementary ends of the viral RNA, creating the distinctive panhandle structure. These RNPs (10-20nm wide) are too large to passively diffuse into the nucleus and therefore, once released from an incoming particle must rely on the active import mechanism of the host cell nuclear pore complex. All proteins in the RNP complex can independently localize to the nucleus due to the presence of nuclear localization signals (NLSs) which mediate their interaction with the nuclear import machinery, including the RanGTPase (Fodor, 2004; Deng et al., 2006). However the signals on NP have been shown to be both sufficient and necessary for the import of viral RNA.

Literature references

Shaw, ML., Palese, P. (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

2005-11-14	Authored	Gillespie, ME.
2006-10-29	Reviewed	Squires, B.

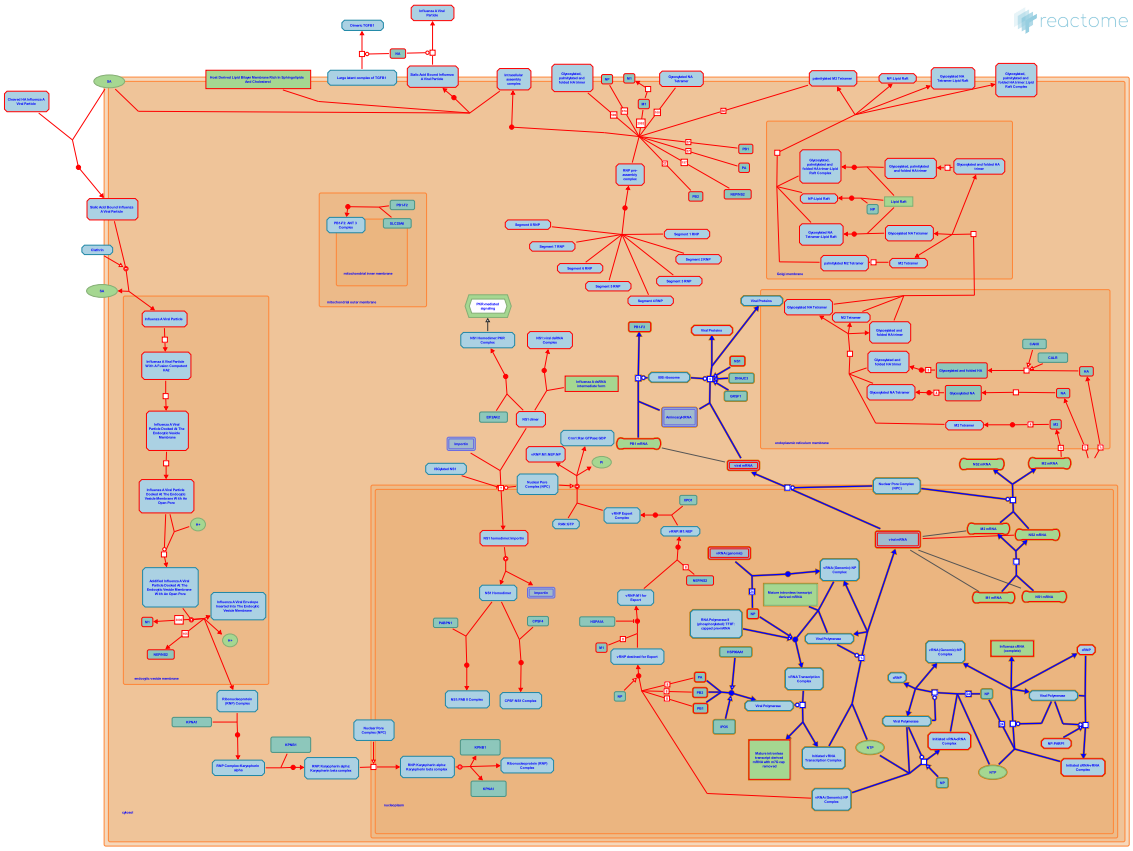
Influenza Viral RNA Transcription and Replication ↗

Location: Influenza Infection

Stable identifier: R-HSA-168273

Compartments: nucleoplasm

Diseases: influenza



In the host cell nucleus, the viral negative-strand RNA (vRNA) serves as a template for the synthesis both of capped, polyadenylated viral messenger RNA and of full-length positive-strand RNA or complementary RNA (cRNA). The cRNA is associated with the same viral proteins as the vRNA. It serves as a template for the synthesis of new vRNA molecules, which in turn serve as a template for mRNA particularly early in infection, and cRNA. Viral RNA polymerase subunits (PB1, PB2, and PA) and nucleoprotein (NP) enter the host cell nucleus and catalyze all three of these reactions. During initial infection, these proteins enter the nucleus as part of the viral RNP complex. After the first round of viral mRNA synthesis (primary transcription) and translation, newly synthesized viral polymerase proteins and NP localize to the nucleus to catalyze further mRNA transcription and vRNA/cRNA replication. Late in the infection process, the synthesis of vRNA and nuclear export of newly synthesized vRNP (vRNA complexed with NP and viral polymerase) is increased relative to transcription (Krug, 1981; Braam, 1983; Kawakami, 1983; Huang, 1990; Cros, 2003; Fodor, 2004; Deng, 2005; Amorim, 2006; reviewed in Neumann, 2004; Engelhardt, 2006; Buolo, 2006).

Literature references

Krystal, M., Palese, P., Huang, TS. (1990). Determination of influenza virus proteins required for genome replication. *J Virol, 64*, 5669-73. ↗

Krug, RM. (1981). Priming of influenza viral RNA transcription by capped heterologous RNAs. *Curr Top Microbiol Immunol, 93*, 125-49. ↗

Braam, J., Krug, RM., Ulmanen, I. (1983). Molecular model of a eucaryotic transcription complex: functions and movements of influenza P proteins during capped RNA-primed transcription. *Cell, 34*, 609-18. ↗

Ishihama, A., Kawakami, K. (1983). RNA polymerase of influenza virus. III. Isolation of RNA polymerase-RNA complexes from influenza virus PR8. *J Biochem (Tokyo), 93*, 989-96. ↗

Editions

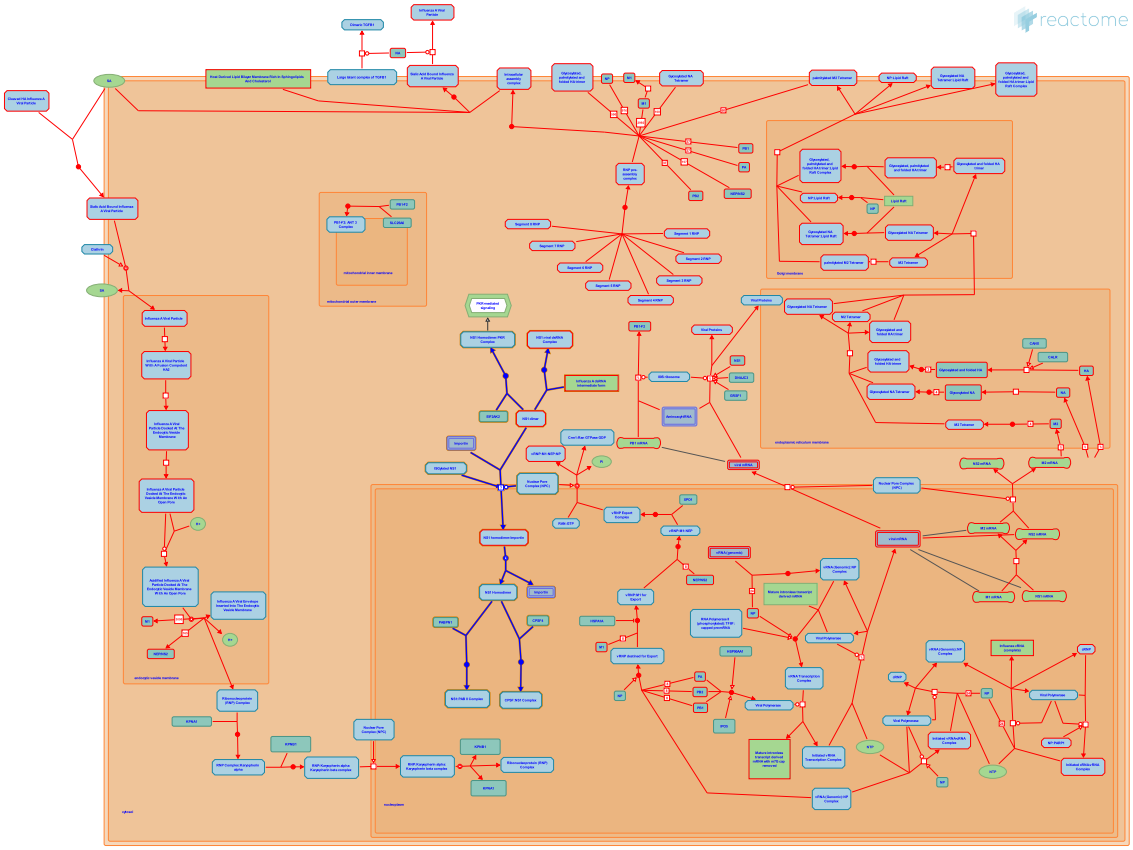
2007-02-13	Authored	Garcia-Sastre, A., Bortz, E.
2007-02-13	Reviewed	Squires, B.

NS1 Mediated Effects on Host Pathways ↗

Location: Influenza Infection

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

Shaw, ML., Palese, P. (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

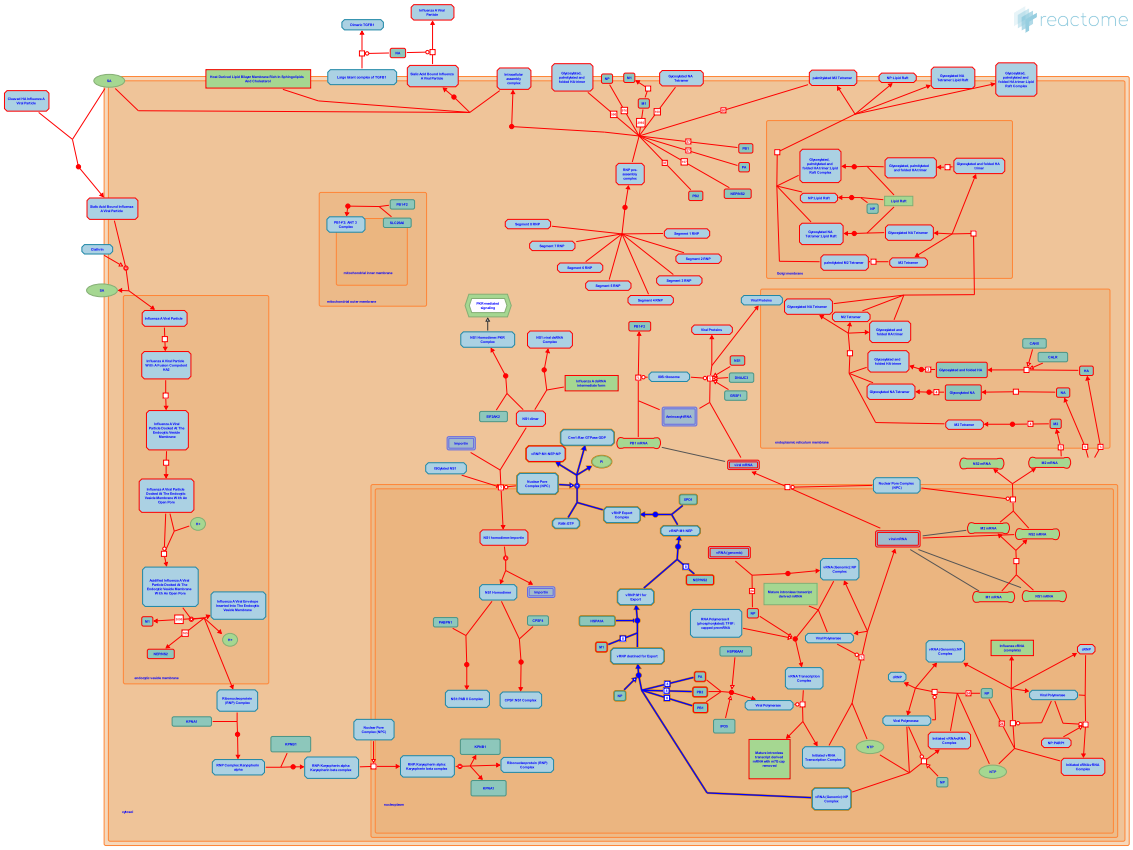
2004-05-12	Reviewed	Gale M, Jr.
2013-11-18	Authored, Edited	Gillespie, ME.

Export of Viral Ribonucleoproteins from Nucleus ↗

Location: Influenza Infection

Stable identifier: R-HSA-168274

Diseases: influenza



Influenza genomic RNA (vRNA), synthesized in the nucleus of the infected host cell, is packaged into ribonucleoprotein (RNP) complexes containing viral polymerase proteins and NP (nucleocapsid). NP trimers bind the sugar phosphate backbone of the vRNA. As influenza viral RNP complexes are too large for passive diffusion out of the nucleus, utilization of the cellular nuclear export machinery is achieved by viral adaptor proteins. Matrix protein (M1) is critical for export of the complex from the nucleus, mediating the interaction of the RNP complex with the viral NEP/NS2 protein, which in turn interacts with host cell CRM1/exportin-1 nuclear export protein (Martin, 1991; O'Neill, 1998; Neumann et al., 2000; Elton, 2001; Cros, 2003; Ye, 2006; reviewed in Boulo, 2006).

Literature references

Baudin, F., Ruigrok, RW., Akarsu, H., Boulo, S. (2006). Nuclear traffic of influenza virus proteins and ribonucleoprotein complexes. *Virus Res, 124*, 12-21. ↗

Neumann, G., Hughes, MT., Kawaoka, Y. (2000). Influenza A virus NS2 protein mediates vRNP nuclear export through NES-independent interaction with hCRM1. *EMBO J, 19*, 6751-8. ↗

Amorim, MJ., Digard, P. (2006). Influenza A virus and the cell nucleus. *Vaccine, 24*, 6651-5. ↗

Editions

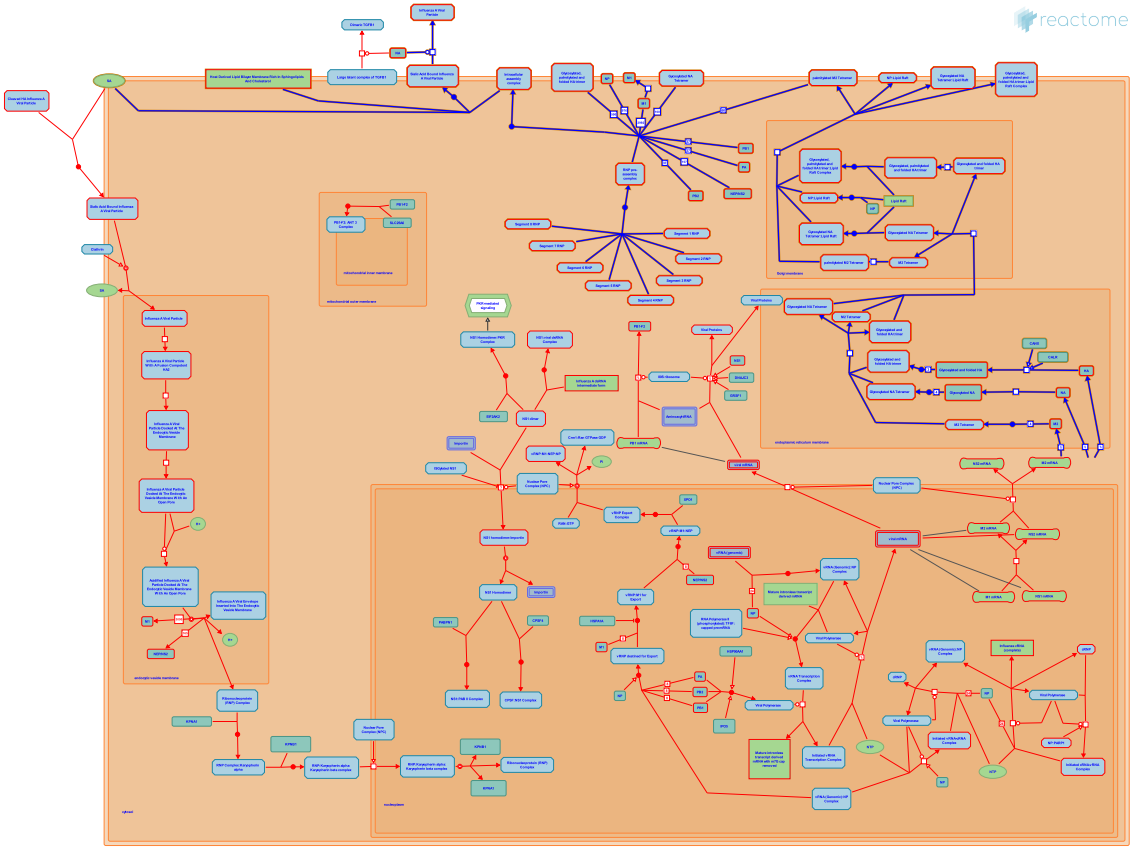
2007-02-13	Authored	Garcia-Sastre, A., Bortz, E.
2007-02-13	Reviewed	Squires, B.

Virus Assembly and Release ↗

Location: Influenza Infection

Stable identifier: R-HSA-168268

Diseases: influenza



Influenza viruses assemble and bud from the apical plasma membrane of polarized cells e.g. lung epithelial cells of the infected host. This asymmetrical process (i.e. apical [Influenza virus] or basolateral [Marburg virus]) is thought to have an important role in viral pathogenesis and tissue tropism. In most cases the individual viral envelope proteins are seen to accumulate at the same polar surface from which virus budding occurs, suggesting that they determine the maturation site

Literature references

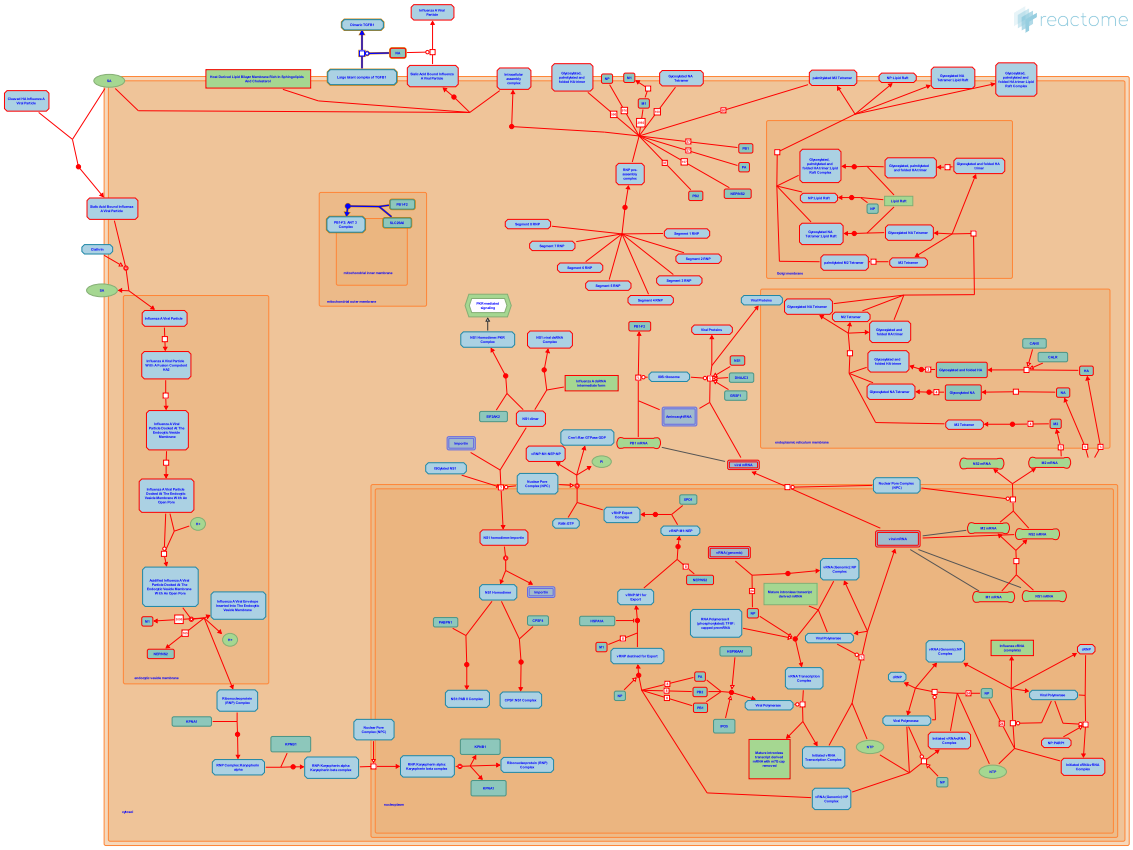
Shaw, ML., Palese, P. (2001). Orthomyxoviridae: The Viruses and Their Replication. *Fields Virology, 5th edition D.M. Knipe and P.M. Howley, Editors. 2006, Lippencott Williams and Wilkins: Philadelphia ISBN-10: 0-7817-6060-7*, 1647-1689. ↗

Influenza Virus Induced Apoptosis ↗

Location: Influenza Infection

Stable identifier: R-HSA-168277

Diseases: influenza



Influenza A virus induces apoptosis in a variety of ways including activation of host TGF-beta by expression of viral NA, M1 and M2 proteins, and by the binding of viral PB1-F2 to host mitochondrial adenine nucleotide translocator 3 (ANT3).

Literature references

Shaw, ML., Palese, P. (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

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

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