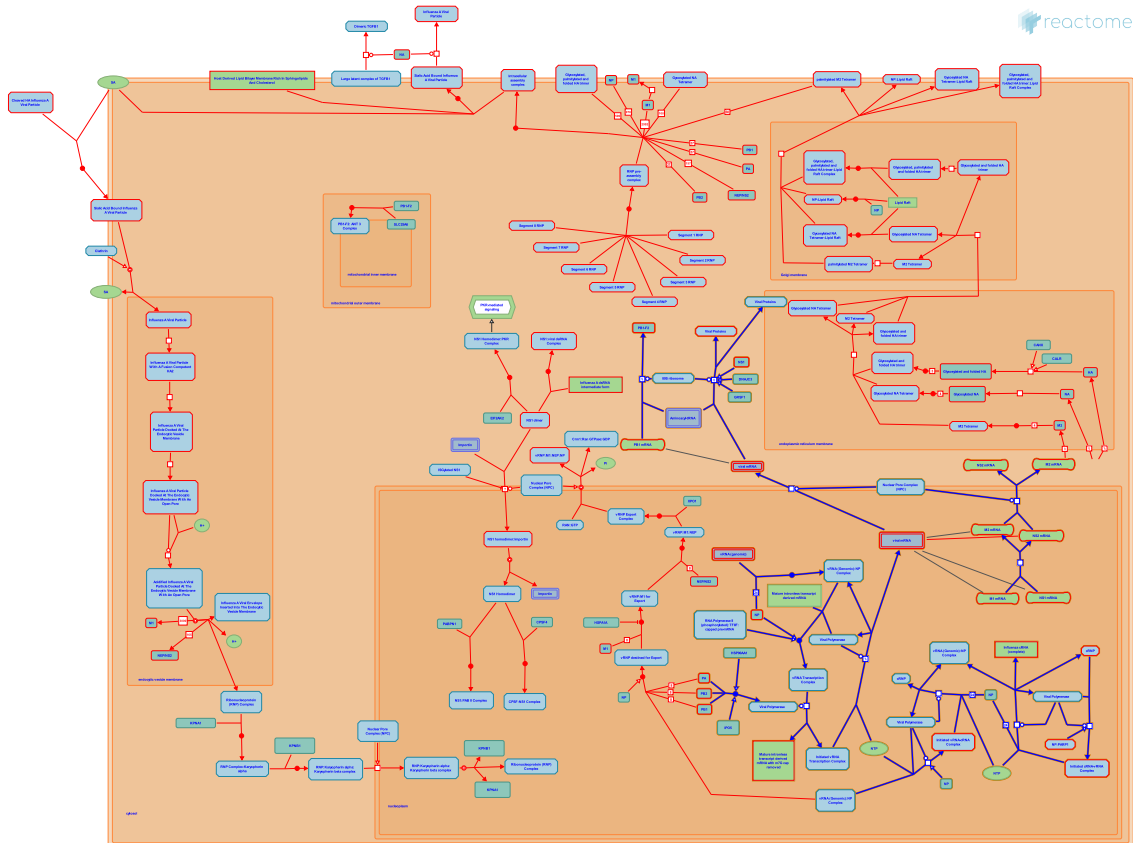


Influenza Viral RNA Transcription and Replication



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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/).

03/05/2024

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).

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Reactome database release: 88

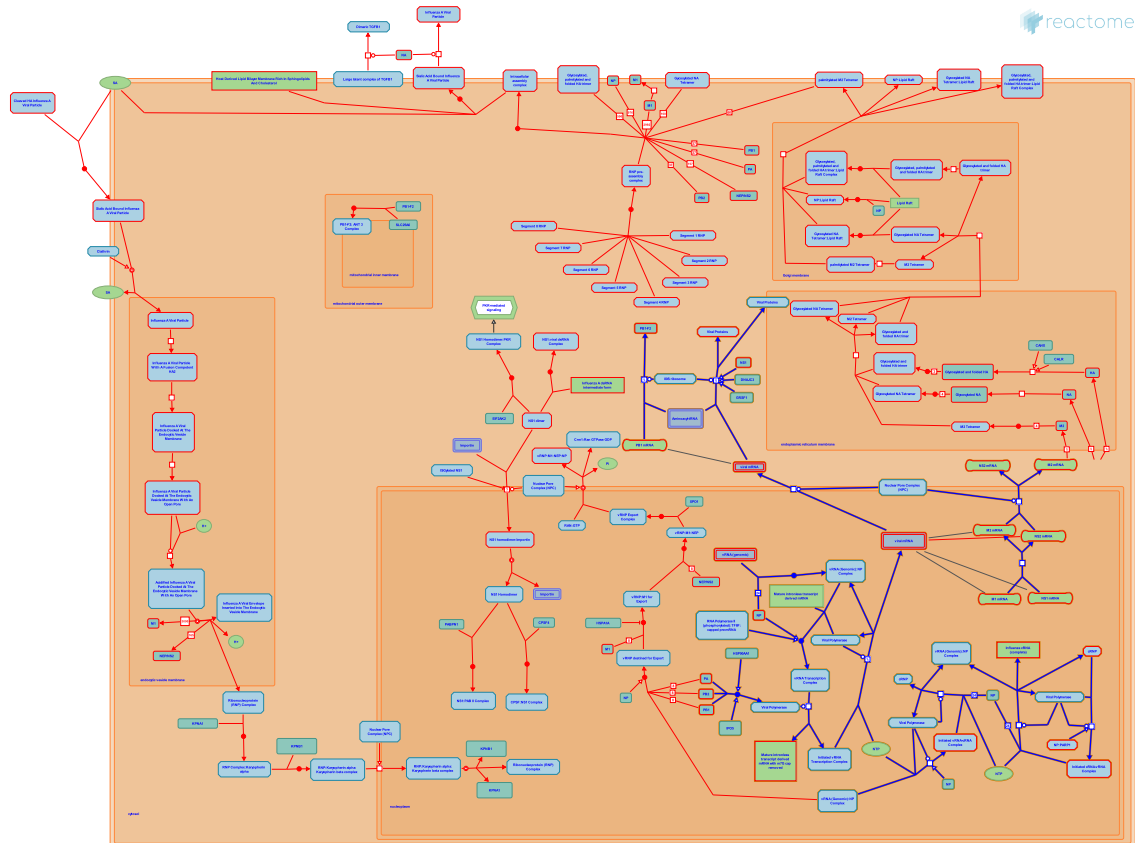
This document contains 6 pathways ([see Table of Contents](#))

Influenza Viral RNA Transcription and Replication ↗

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).

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

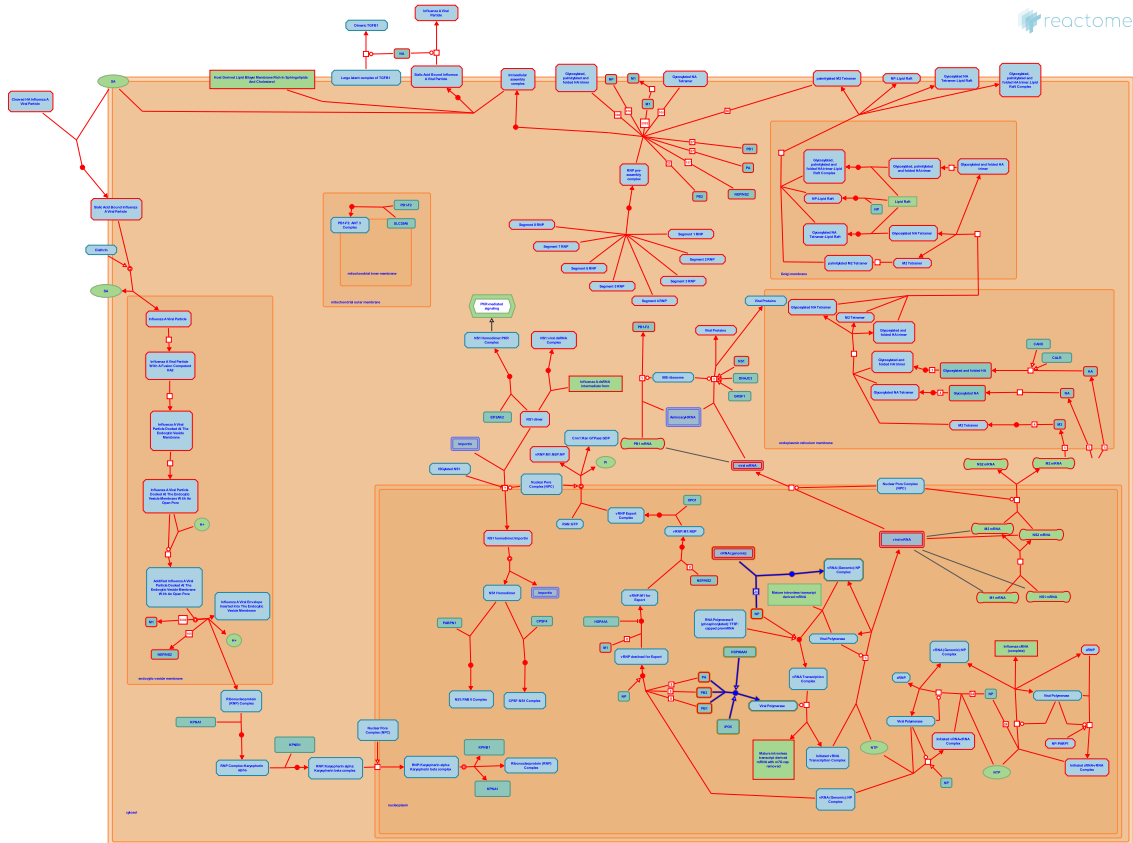
vRNP Assembly ↗

Location: Influenza Viral RNA Transcription and Replication

Stable identifier: R-HSA-192905

Compartments: nucleoplasm

Diseases: influenza



For each of eight gene segments, a viral ribonucleoprotein (vRNP), containing a viral negative-sense RNA (vRNA) segment complexed with nucleoprotein (NP) and the trimeric influenza polymerase (PB1, PB2, and PA), is assembled in the nucleus (Braam, 1983; Jones, 1986; Cros, 2003; reviewed in Buolo, 2006). The vRNP functions in three modes (reviewed in Mikulasova, 2000; Neumann, 2004): (1) transcription, which synthesizes viral messenger RNA from the vRNA template using as primers 5' ends of cellular mRNAs containing the cap; (2) replication, which produces positive-sense complementary RNA (cRNA) and subsequently vRNA, both complexed with NP and the trimeric polymerase; or (3), the vRNP is exported from the nucleus into the cytoplasm and is incorporated into assembling virions at the plasma membrane.

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

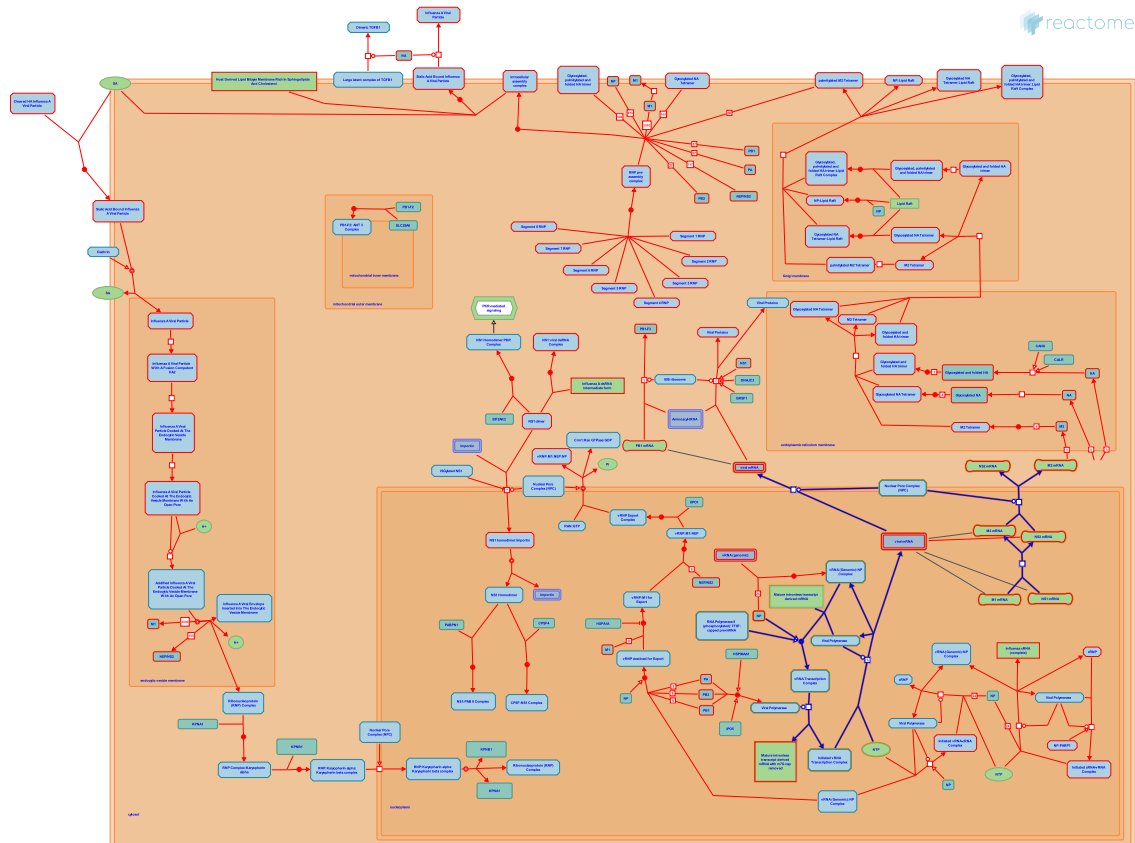
Viral Messenger RNA Synthesis ↗

Location: Influenza Viral RNA Transcription and Replication

Stable identifier: R-HSA-168325

Compartments: nucleoplasm

Diseases: influenza



Like the mRNAs of the host cell, influenza virus mRNAs are capped and polyadenylated (reviewed in Neumann, 2004). The methylated caps, however, are scavenged from host cell mRNAs and serve as primers for viral RNA synthesis, a process termed 'cap-snatching' (Krug, 1981; Hagen, 1994). The PB2 polymerase protein binds the cap, activating endonucleolytic cleavage of the host mRNA by PB1. The 3' poly-A tracts on viral messages are generated by polymerase stuttering on poly-U tracts near the 5' end of the template vRNA (Robertson, 1981; Zheng, 1999). The second process allows polyadenylation of viral mRNAs when the host cell polyadenylation process has been inhibited (Engelhardt, 2006; Amorim, 2006). Notably, early transcripts (including NP and NS1) accumulate in the cytoplasm before late transcripts (M1, HA, and NS2), and in varying abundances, suggesting additional control mechanisms regulating viral gene expression (Shapiro, 1987; Hatada, 1989; Amorim, 2006).

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

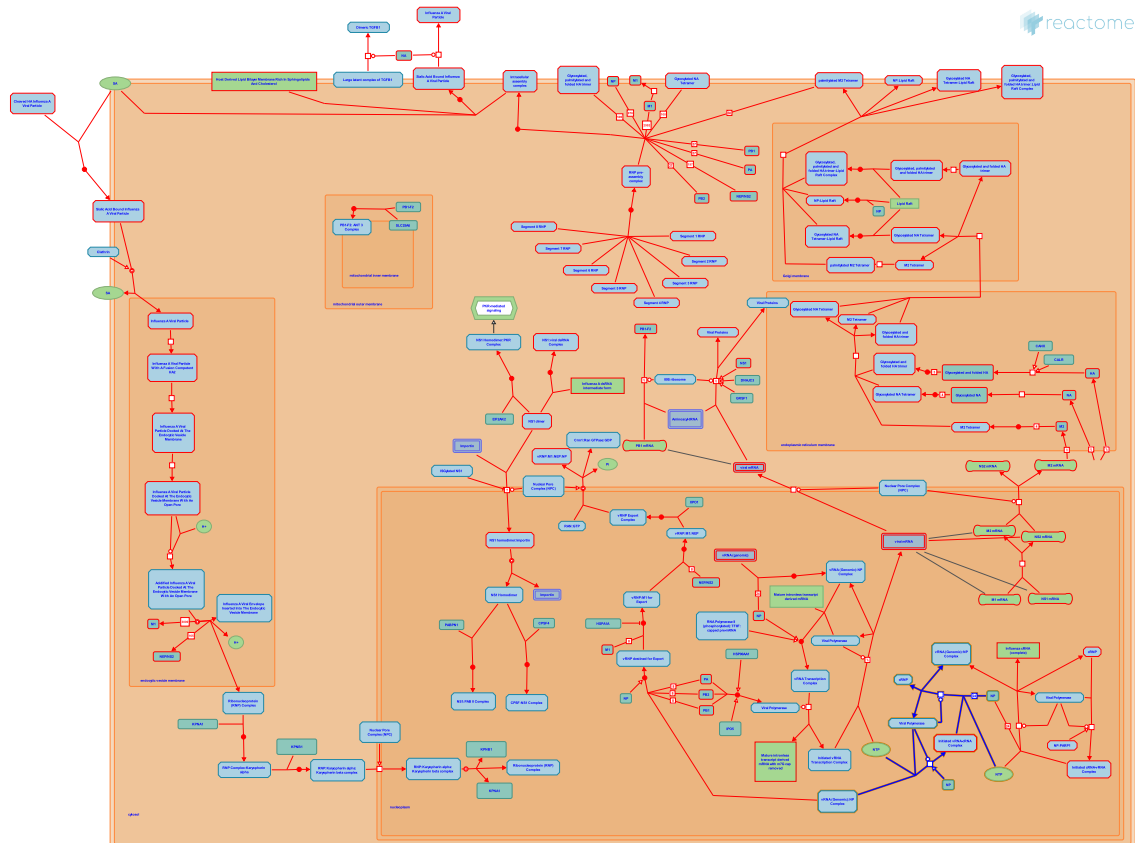
cRNA Synthesis ↗

Location: Influenza Viral RNA Transcription and Replication

Stable identifier: R-HSA-192869

Compartments: nucleoplasm

Diseases: influenza



Synthesis of full length complementary viral RNA (cRNA) requires that vRNA transcription initiates without the help of a host cell methyl RNA cap as a primer (Crow, 2004; Vreede, 2004; Deng, 2006), and that it proceeds to the 5' end of the vRNA template without stuttering on the sub-terminal poly-U sequence. Free viral NP protein appears to play a central role in enabling both of these features of cRNA synthesis, although the molecular details of its role remain unclear (Shapiro, 1988; Medcalf, 1999; Mullin, 2004).

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Editions

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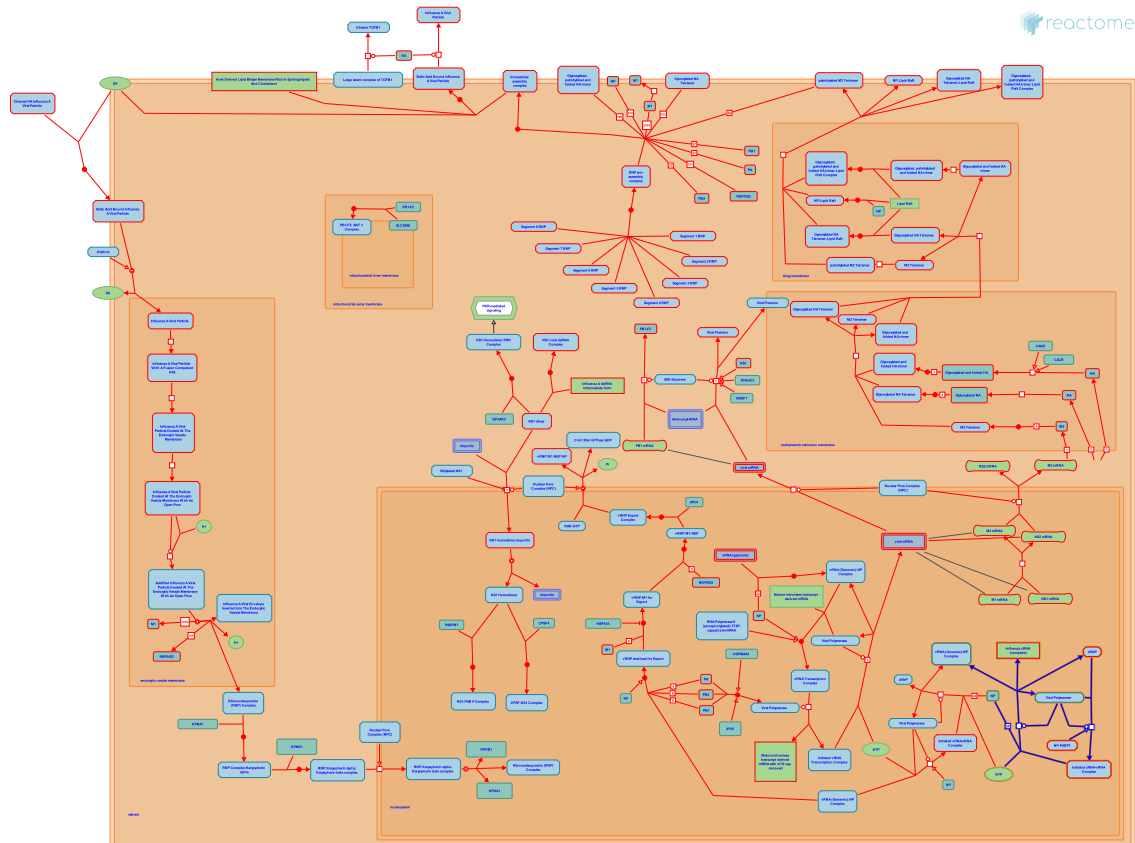
vRNA Synthesis ↗

Location: Influenza Viral RNA Transcription and Replication

Stable identifier: R-HSA-192814

Compartments: nucleoplasm

Diseases: influenza



The synthesis of full-length negative strand viral RNA from a cRNA template is believed to follow the same principles as the synthesis of cRNA from a vRNA template. The cRNA, complexed with viral nucleocapsid (NP) protein, is used as template by the trimeric viral polymerase (Pritlove, 1995; Vreede, 2004; Crow, 2004), and newly synthesized vRNA molecules are immediately packaged with NP molecules to form ribonucleoprotein complexes (Vreede, 2004). There is some evidence that the production of vRNA-containing vRNP occurs in the nuclear matrix as well as the nucleoplasm (Takizawa, 2006).

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Editions

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2007-02-13	Reviewed	Squires, B.

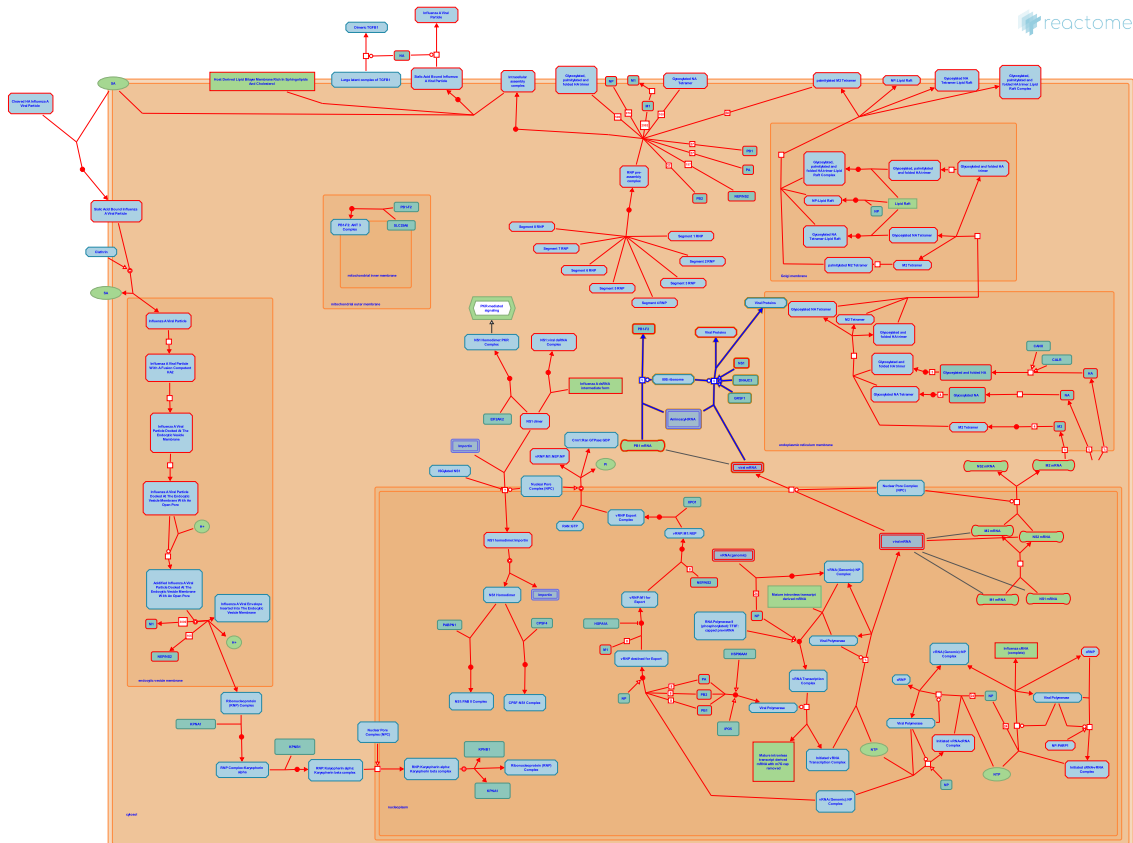
Viral mRNA Translation ↗

Location: Influenza Viral RNA Transcription and Replication

Stable identifier: R-HSA-192823

Compartments: cytosol

Diseases: influenza



Spliced and unspliced viral mRNA in the cytoplasm are translated by host cell ribosomal translation machinery (reviewed in Kash, 2006). At least ten viral proteins are synthesized: HA, NA, PB1, PB2, PA, NP, NS1, NEP/NS2, M1, and M2. Viral mRNA translation is believed to be enhanced by conserved 5'UTR sequences that interact with the ribosomal machinery and at least one cellular RNA-binding protein, G-rich sequence factor 1 (GRSF-1), has been found to specifically interact with the viral 5' UTRs. (Park, 1995; Park, 1999). The viral NS1 protein and the cellular protein P58(IPK) enhance viral translation indirectly by preventing the activation of the translational inhibitor PKR (Salvatore, 2002; Goodman, 2006). The viral NS1 protein has also been proposed to specifically enhance translation through interaction with host poly(A)-binding protein 1 (PABP1) (Burgui, 2003). Simultaneously, host cell protein synthesis is downregulated in influenza virus infection through still uncharacterized mechanisms (Katze, 1986; Garfinkel, 1992; Kash, 2006). In most human influenza A strains (such as PR8), the PB1 mRNA segment is capable of producing a second protein, PB1-F2, from a short +1 open reading frame initiating downstream of the PB1 ORF initiation codon (Chen, 2001).

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Editions

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

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