Orthomyxoviruses

Family: *Orthomyxoviridae*

Genus	Type species
Influenza A virus	A/PR/8/34(H1N1)
Influenza B virus	B/Lee/40
Influenza C virus	C/California/78
Thogotovirus	Thogoto virus
Isavirus	Infectious salmon anemia virus

Influenza viruses are the causative agents of a highly contagious, often serious acute respiratory illness. The importance of this disease has been an impetus for research on the virus. Influenza viruses are unusual among RNA viruses because all viral RNA synthesis occurs in the cell nucleus. Initiation of viral mRNA synthesis with a capped primer derived from host cell mRNA was first described in cells infected with influenza viruses. The viral genomes undergo extensive reassortment and variation, and are expressed via a remarkable panoply of unusual strategies, including RNA splicing, overlapping reading frames, and leaky scanning.

Figure 8 Structure and genomic organization of the orthomyxovirus influenza A virus. (A) The virion. (Left) Electron micrograph of negatively stained influenza A virus particles. Courtesy of P. Palese, Mt. Sinai School of Medicine. (Right) Diagram indicating the location of the nine virion proteins, the viral envelope, and the eight genomic RNA segments. **(B) Genome organization.** The (–) strand RNA genome comprises eight segments, each of which encodes at least one viral protein as shown. The two smallest genomic RNA segments, 7 and 8, each code for two proteins, because some fraction of the (+) strand mRNA copies are spliced by host cell enzymes. The NS1 (nonstructural) protein is so named because it is not incorporated into virus particles. An accessory protein with proapoptotic activity, PB1-F2, can be produced from the PB1 RNA. Blue boxes containing the letter C denote the capped host mRNA fragments that serve as primers during mRNA synthesis.

Figure 9 Single-cell reproductive cycle of influenza A virus. The virion binds to a sialic acid-containing cellular surface protein or lipid and enters the cell via receptor-mediated endocytosis **(1)**. Upon acidification of the vesicle, the viral membrane fuses with the membrane of the vesicle, releasing the viral nucleocapsids into the cytoplasm **(2)**. The viral nucleocapsids containing (–) strand genomic RNA, multiple copies of the NP protein, and the P proteins are transported into the nucleus **(3)**. The (–) strand RNA is copied by virion RNA polymerase into viral mRNA, using the capped 5′ ends of host pre-mRNAs (or mRNAs) as primers to initiate synthesis **(4)**. The mRNAs are transported to the cytoplasm **(5)**, following splicing in the case of the mRNAs encoding NEP and M2 **(6)**. The mRNAs specifying the viral membrane proteins (HA, NA, M2) are translated by ribosomes bound to the endoplasmic reticulum (ER) **(7)**. These proteins enter the host cell's secretory pathway, where HA and NA are glycosylated. All other mRNAs are translated by ribosomes in the cytoplasm **(8** and **9)**. The PA, PB1, PB2, and NP proteins are imported into the nucleus **(10a)**, where they participate in the synthesis of full-length (+) strand RNAs **(11)** and then (–) strand genomic RNAs **(12)**, both of which are synthesized in the form of nucleocapsids. Some of the newly synthesized (–) strand RNAs enter the pathway for mRNA synthesis **(13)**. The M1 protein and the NS1 protein are transported into the nucleus **(10b)**. Binding of the M1 protein to newly synthesized (–) strand RNAs shuts down viral mRNA synthesis and, in conjunction with the NEP protein, induces export of progeny nucleocapsids to the cytoplasm **(14)**. The HA, NA, and M2 proteins are transported to the cell surface **(15)** and become incorporated into the plasma membrane **(16)**. The virion nucleocapsids associated with the M1 protein **(17)**, and the NEP protein **(18)**, are transported to the cell surface and associate with regions of the plasma membrane that contain the HA and NA proteins. Assembly of virions is completed at this location by budding from the plasma membrane **(19)**.