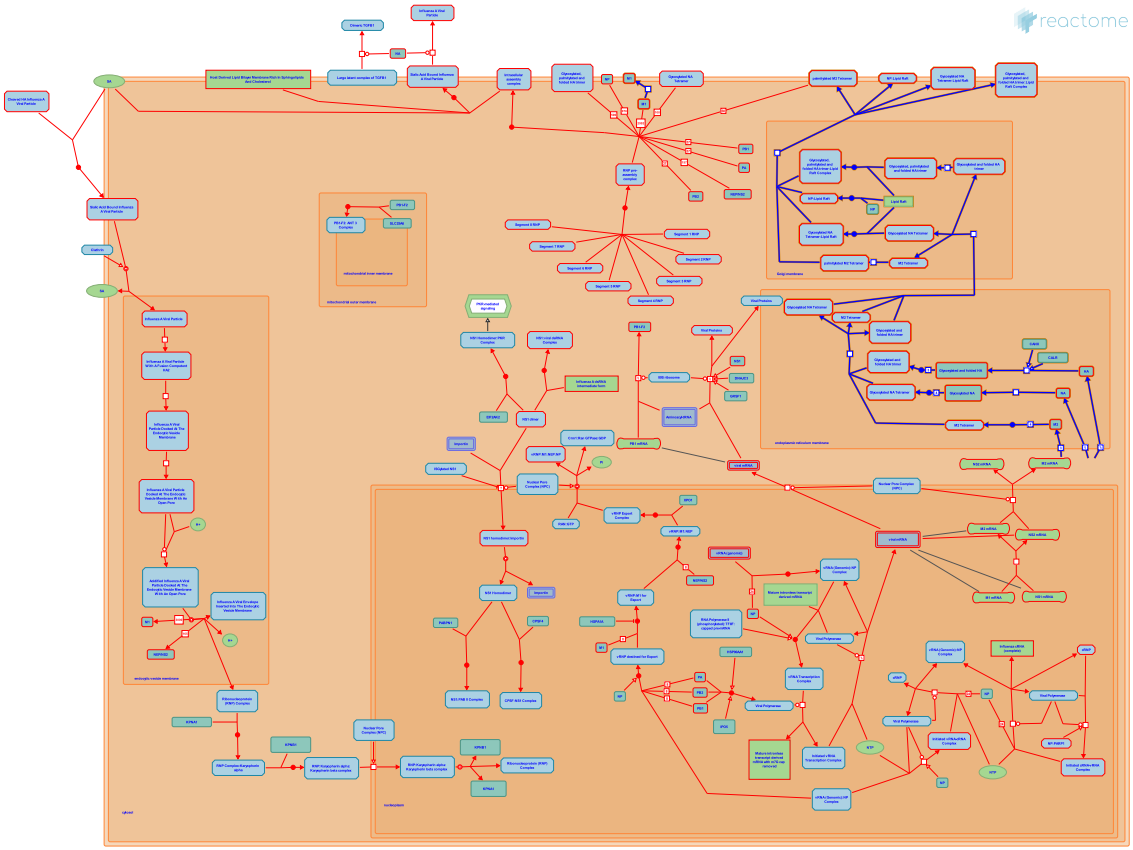
Assembly of Viral Components at the Budding Site



Rush, MG., Squires, B., Steel, J.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

20/09/2024

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).

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: 89

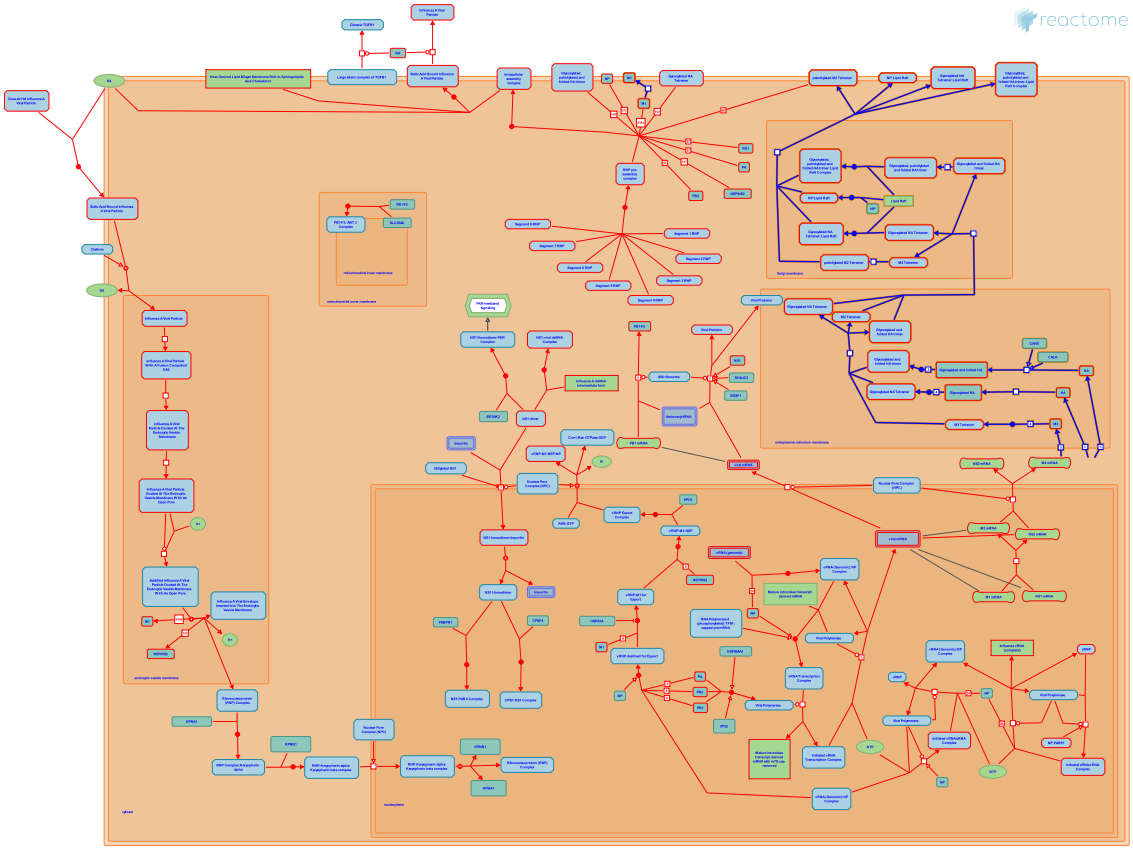
This document contains 2 pathways and 15 reactions (see Table of Contents)

Assembly of Viral Components at the Budding Site ↗

Stable identifier: R-HSA-168316

Compartments: plasma membrane

Diseases: influenza



Following synthesis on membrane-bound ribosomes, the three viral integral membrane proteins, HA (hemagglutinin), NA (neuraminidase) and M2 (ion channel) enter the host endoplasmic reticulum (ER) where all three are folded and HA and NA are glycosylated. Subsequently HA is assembled into a trimer. HA, NA and M2 are transported to the Golgi apparatus where cysteine residues on HA and M2 are palmitoylated. Furin cleaves HA into HA1 and HA2 subunits and all three proteins are directed to the virus assembly site on the apical plasma membrane via apical sorting signals. The signals for HA and NA reside on the transmembrane domains (TMD) while the sorting signal for M2 is not yet characterized. The TMDs of HA and NA also contain the signals for lipid raft association. Lipid rafts are non-ionic detergent-resistant lipid microdomains within the plasma membrane that are rich in sphingolipids and cholesterol. Examination of purified virus particles indicates that influenza virus buds preferentially from these microdomains.

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

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

M2 protein synthesis ↗

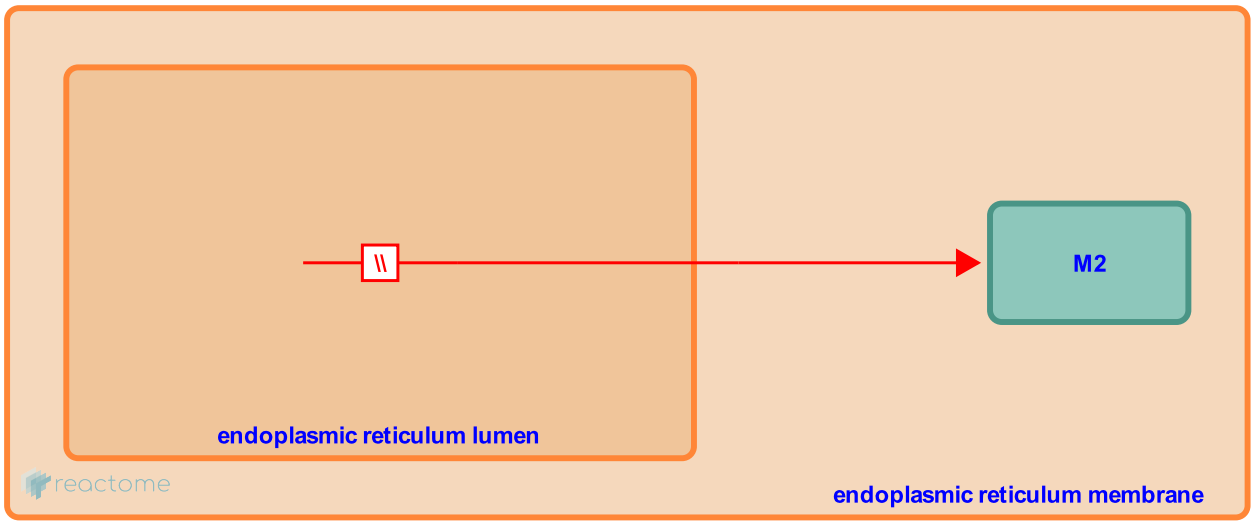
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-195733

Type: omitted

Compartments: endoplasmic reticulum lumen

Diseases: influenza



The integral membrane protein M2 is synthesized on membrane-bound ribosomes and subsequently transported across the ER, where it is folded and assembled into a tetramer.

Followed by: Assembly of M2 tetramers

Literature references

Doms, RW., Helenius, A., Lamb, RA., Rose, JK. (1993). Folding and assembly of viral membrane proteins. *Virology, 193*, 545-62. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Assembly of M2 tetramers ↗

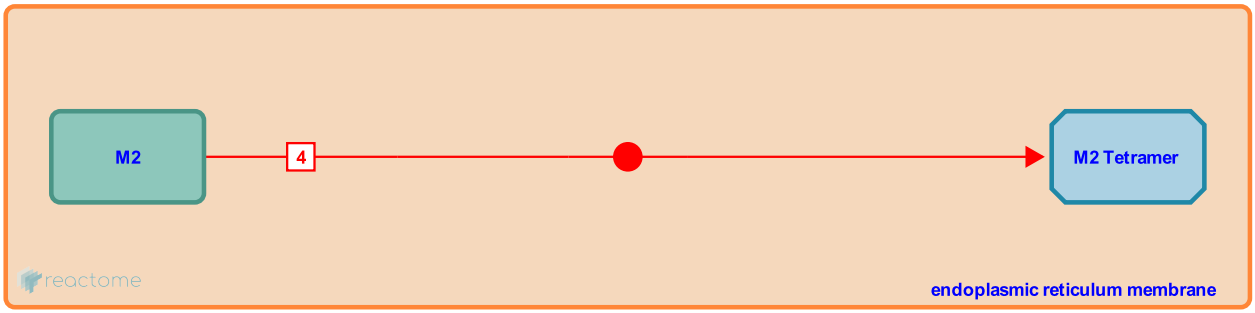
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-188544

Type: binding

Compartments: endoplasmic reticulum membrane

Diseases: influenza



The M2 from influenza A virus is a 97-residue protein with a single transmembrane helix that associates to form a tetramer in the endoplasmic reticulum (Salom et al, 2000). A 15-20-residue segment C-terminal to the membrane-spanning region has been postulated to aid in the stabilization of the tetrameric assembly (Kochendoerfer et al 1999).

Preceded by: M2 protein synthesis

Followed by: Transport of HA trimer, NA tetramer and M2 tetramer from the endoplasmic reticulum to the Golgi Apparatus

Literature references

DeGrado, WF., Salom, D., Hill, BR., Lear, JD. (2000). pH-dependent tetramerization and amantadine binding of the transmembrane helix of M2 from the influenza A virus. *Biochemistry, 39*, 14160-70. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Neuraminidase (NA) synthesis ↗

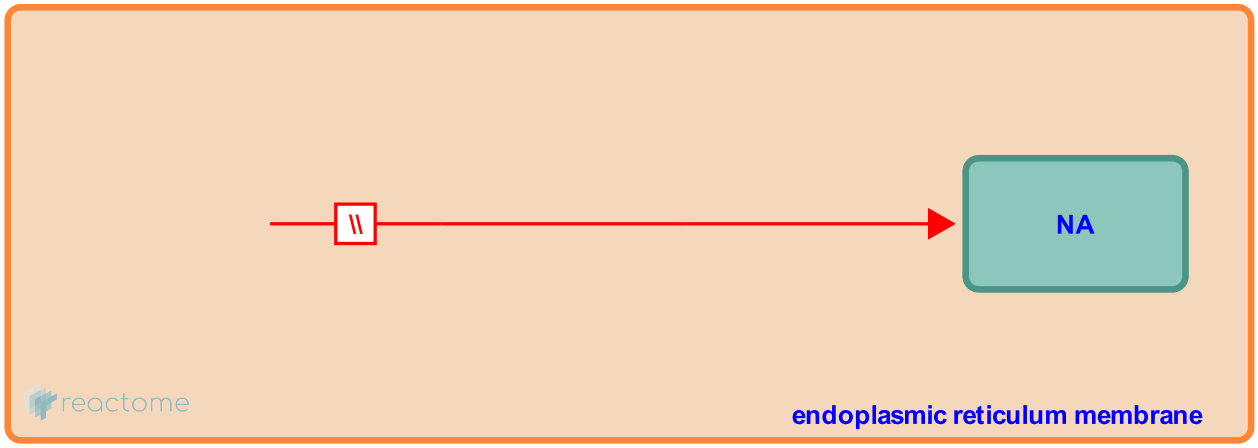
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-195734

Type: omitted

Compartments: endoplasmic reticulum membrane

Diseases: influenza



The integral membrane protein NA is synthesized on membrane-bound ribosomes and subsequently transported across the ER where it is folded and glycosylated. Subsequently NA is assembled into a tetramer.

Followed by: Glycosylation of NA

Literature references

Doms, RW., Helenius, A., Lamb, RA., Rose, JK. (1993). Folding and assembly of viral membrane proteins. *Virology, 193*, 545-62. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
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Glycosylation of NA ↗

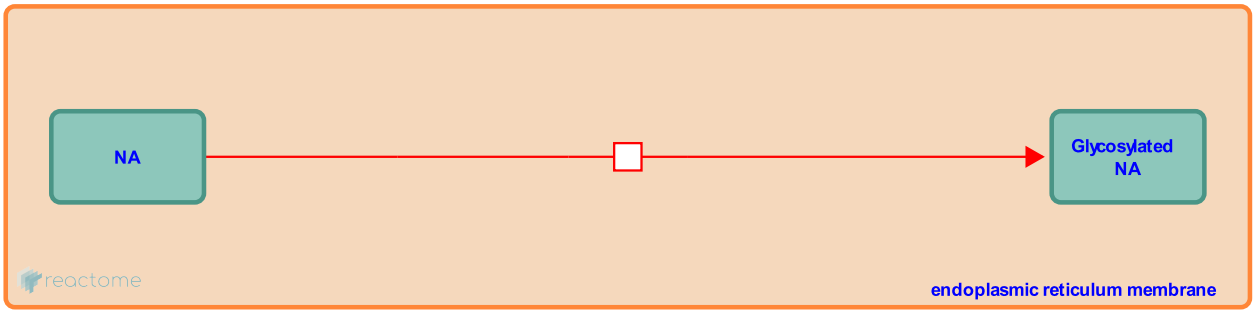
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-169919

Type: transition

Compartments: endoplasmic reticulum membrane

Diseases: influenza



Glycosylation of NA occurs within the endoplasmic reticulum and is believed to be neccessary for proper tetramerization of the NA dimers. Sugar residues become attached to four of the five potential glycosylation sites in the head of N1 neuraminidase (Hausman et al., 1997).

Preceded by: Neuraminidase (NA) synthesis

Followed by: Assembly of NA tetramers

Literature references

Klenk, HD., Garten, W., Hausmann, J., Kretzschmar, E. (1997). Biosynthesis, intracellular transport and enzymatic activity of an avian influenza A virus neuraminidase: role of unpaired cysteines and individual oligosaccharides. *J Gen Virol*, 3233-45. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Assembly of NA tetramers ↗

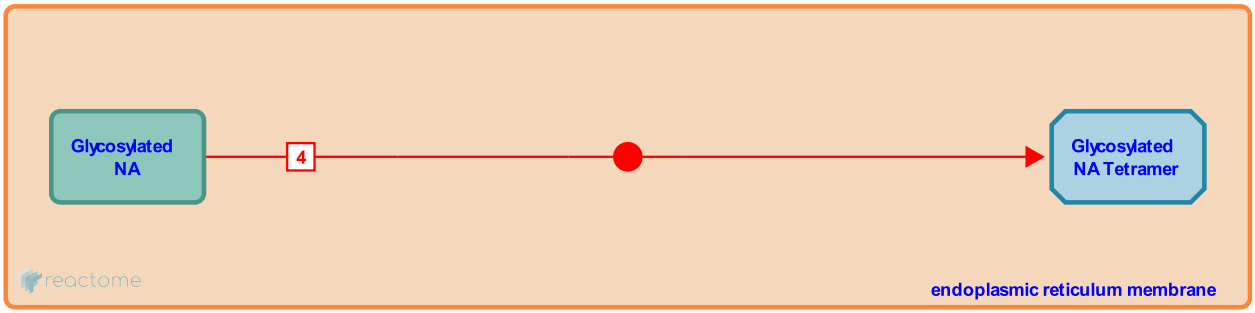
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-169847

Type: binding

Compartments: endoplasmic reticulum membrane

Diseases: influenza



Tetramerisation of the NA occurs in the ER following an initial dimerisation step. Tetramerisation is believed to be dependant on glycosylation of the NA molecules

Preceded by: Glycosylation of NA

Followed by: Transport of HA trimer, NA tetramer and M2 tetramer from the endoplasmic reticulum to the Golgi Apparatus

Literature references

Webster, RG., Saito, T., Taylor, G. (1995). Steps in maturation of influenza A virus neuraminidase. *J Virol, 69,* 5011-7. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Hemagglutinin (HA) protein synthesis ↗

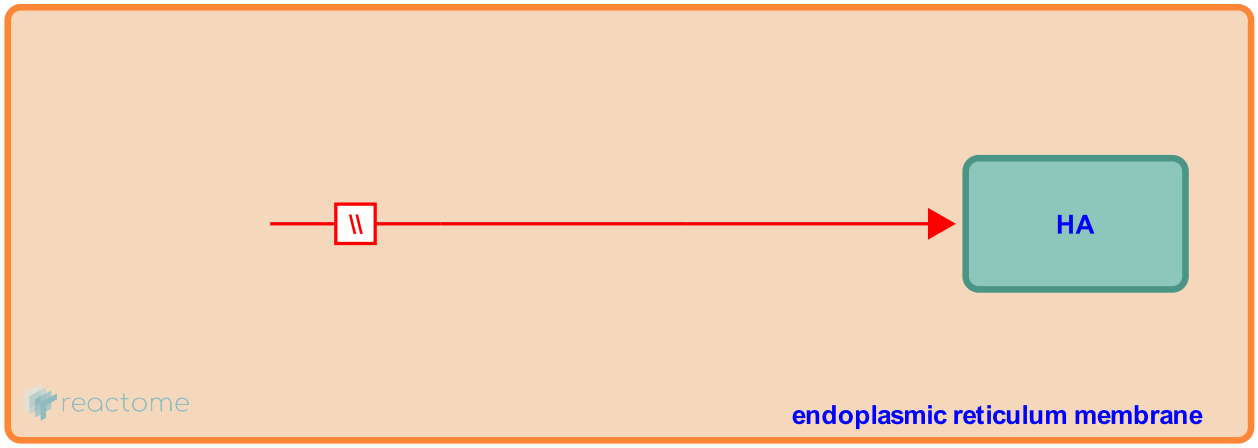
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-168884

Type: omitted

Compartments: endoplasmic reticulum membrane

Diseases: influenza



The integral membrane protein HA is synthesized on membrane-bound ribosomes and subsequently transported across the endoplasmic reticulum, where it is folded, glycosylated, and assembled into a trimer.

Followed by: Glycosylation and Folding of HA

Literature references

Doms, RW., Helenius, A., Lamb, RA., Rose, JK. (1993). Folding and assembly of viral membrane proteins. *Virology, 193*, 545-62. ↗

Editions

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2007-05-01	Authored	Steel, J.

Glycosylation and Folding of HA ↗

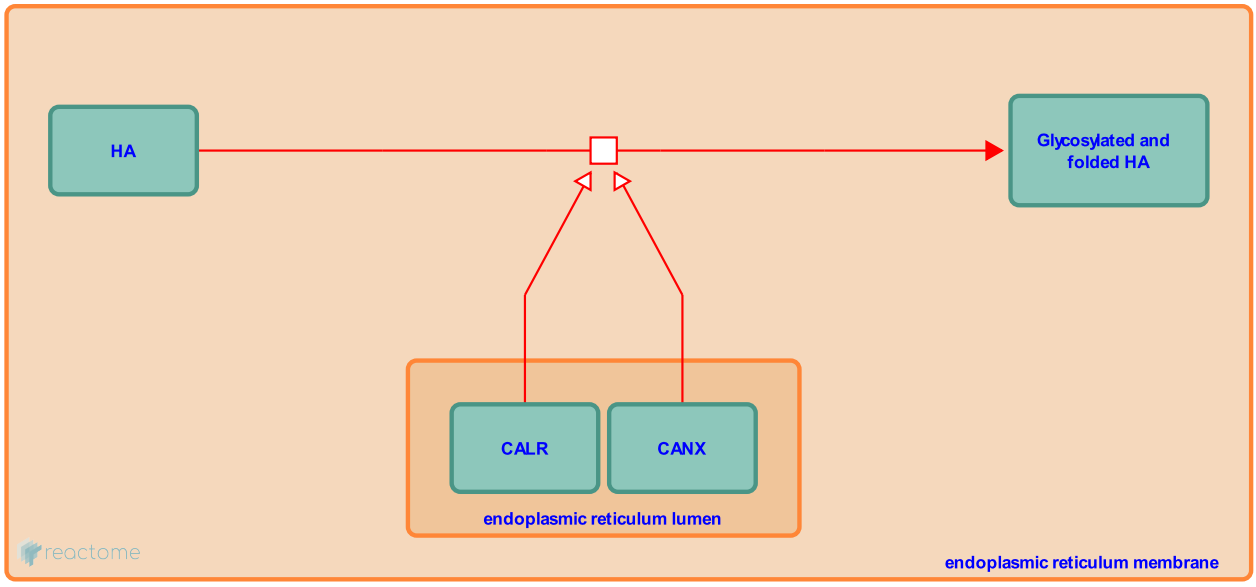
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-169921

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen

Diseases: influenza



The ectodomain of HA is translocated into the ER lumen, where it undergoes a series of folding events mediated by the formation of disulfide bonds and glycosylation reactions. The formation of a discrete intermediate species of highly folded monomeric protein preceeds trimerisation. The folding process is efficient and rapid, with greater than 90% of the protein trafficked to the golgi apparatus; and mature HA0 subunits appearing in a matter of a few minutes. Calnexin and calreticulin have been identified as cellular lectins which interact transiently with newly synthesized HA by attaching to partially trimmed N-linked oligosaccharides (Herbert et al., 1997), facilitating correct folding of the HA molecule.

Preceded by: Hemagglutinin (HA) protein synthesis

Followed by: Trimerization of HA

Literature references

Helenius, A., Molinari, M. (2000). Chaperone selection during glycoprotein translocation into the endoplasmic reticulum. *Science, 288*, 331-3. ↗

Kurowski, B., Daniels, R., Johnson, AE., Hebert, DN. (2003). N-linked glycans direct the cotranslational folding pathway of influenza hemagglutinin. *Mol Cell, 11*, 79-90. ↗

Editions

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2007-05-01	Authored	Steel, J.

Trimerization of HA ↗

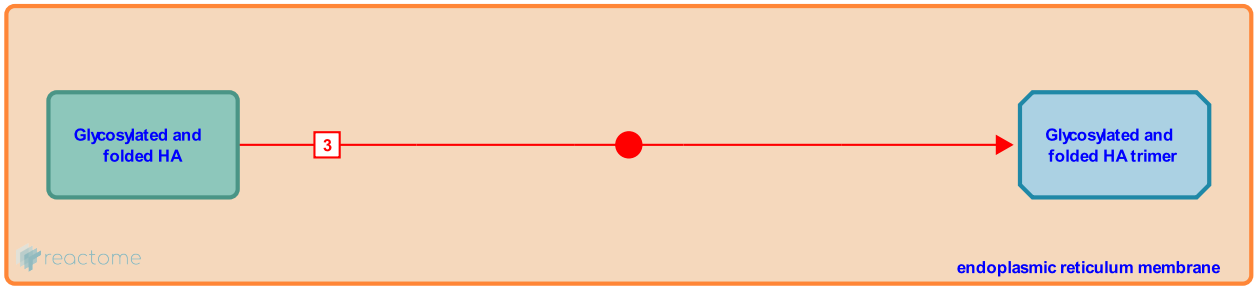
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-168875

Type: binding

Compartments: endoplasmic reticulum membrane

Diseases: influenza



Trimerisation of the fully folded and fully oxidised HA monomer is thought to occur in the endoplasmic reticulum and ERGIC compartment, following dissociation of HA from calnexin. Trimerisation is generally thought to be the final step in HA maturation occurring in the endoplasmic reticulum before transport to the Golgi apparatus, although Yewdell et al (1988) provide data suggesing that trimerisation may occur within the Golgi.

Preceded by: Glycosylation and Folding of HA

Followed by: Transport of HA trimer, NA tetramer and M2 tetramer from the endoplasmic reticulum to the Golgi Apparatus

Literature references

Doms, RW., Helenius, A., Lamb, RA., Rose, JK. (1993). Folding and assembly of viral membrane proteins. *Virology, 193*, 545-62. ↗

Hammond, C., Helenius, A., Tatu, U. (1995). Folding and oligomerization of influenza hemagglutinin in the ER and the intermediate compartment. *EMBO J, 14*, 1340-8. ↗

Sambrook, J., Gething, MJ., McCammon, K. (1986). Expression of wild-type and mutant forms of influenza hemagglutinin: the role of folding in intracellular transport. *Cell, 46*, 939-50. ↗

Editions

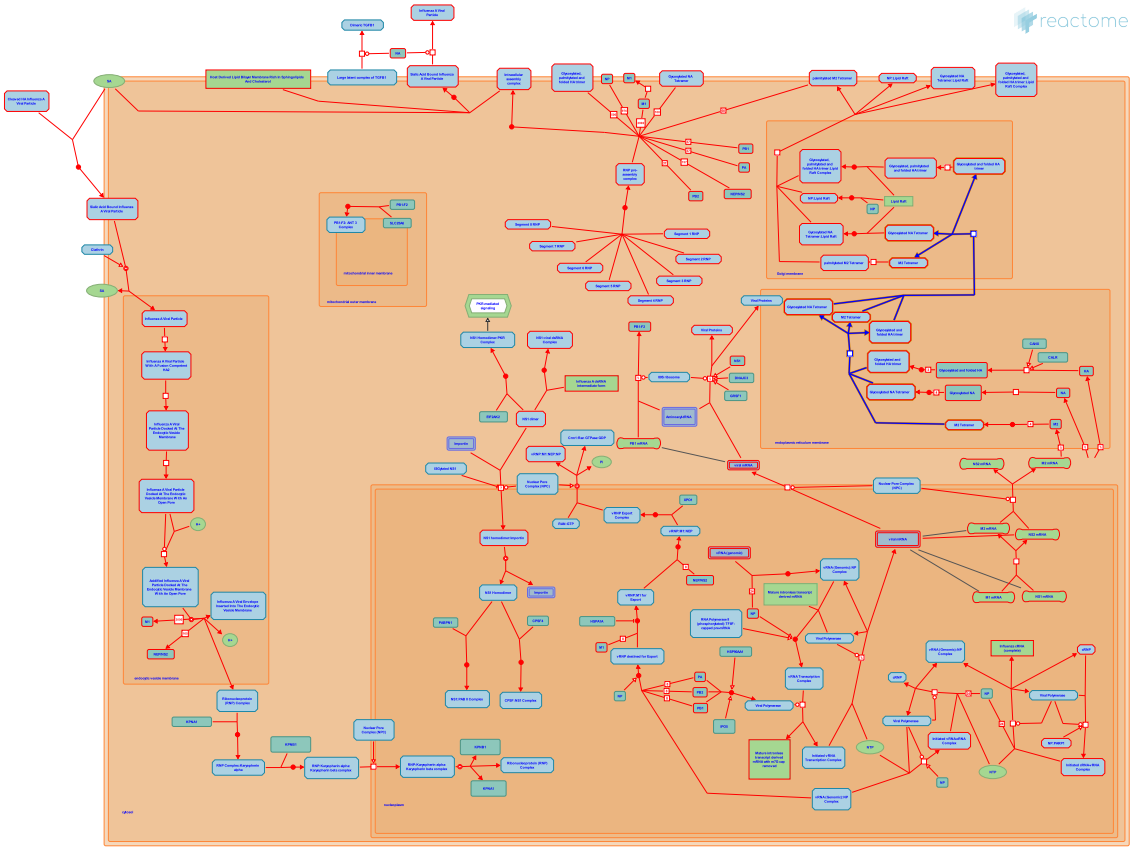
2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Transport of HA trimer, NA tetramer and M2 tetramer from the endoplasmic reticulum to the Golgi Apparatus ↗

Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-168874

Diseases: influenza



Processed viral proteins are transported from the endoplasmic reticulum to the Golgi apparatus.

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

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Palmitoylation of cysteine residues on HA in the cis-Golgi network ↗

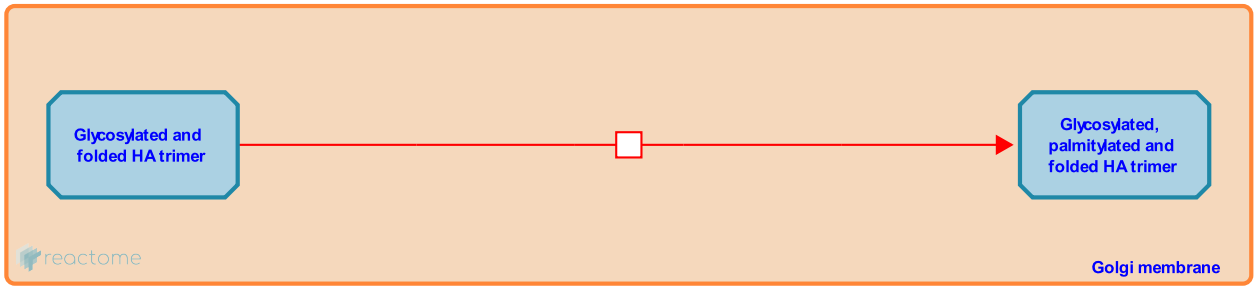
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-168858

Type: transition

Compartments: Golgi membrane

Diseases: influenza



The hemagglutinin of influenza virus is palmitoylated with long-chain fatty acids.
Palmitoylation of HA is believed to occur in the cis golgi network (Veit 1993), shortly after trimerisation of the molecule, and before cleavage of the HA into HA1 and HA2. HA is palmitoylated through thioester linkages at three cysteine residues located in the cytoplasmic domain and at the carboxy-terminal end of the transmembrane region. Lack of acylation has no obvious influence on the biological activities of HA.

Followed by: Association of HA into rafts

Literature references

Kuroda, K., Klenk, HD., Garten, W., Kretzschmar, E., Veit, M., Rott, R. et al. (1991). Site-specific mutagenesis identifies three cysteine residues in the cytoplasmic tail as acylation sites of influenza virus hemagglutinin. *J Virol, 65*, 2491-500. ↗

Veit, M., Schmidt, MF. (1993). Timing of palmitoylation of influenza virus hemagglutinin. *FEBS Lett, 336*, 243-7. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Palmitoylation of cysteine residues on M2 in the cis-golgi network ↗

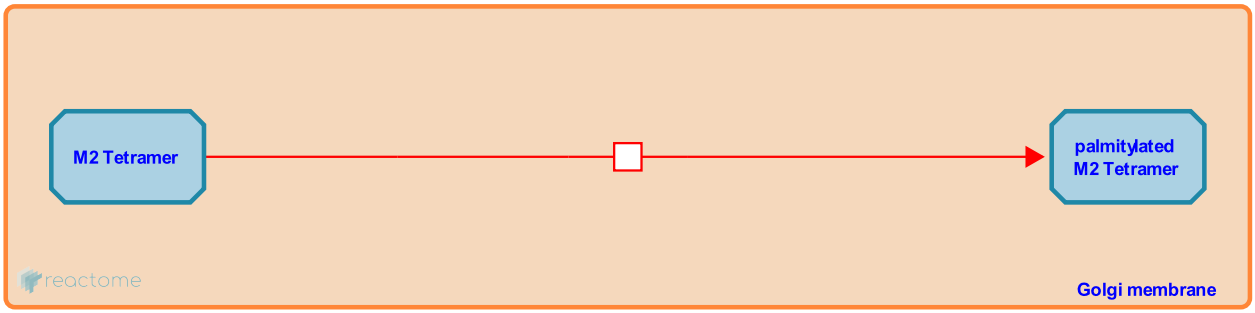
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-195739

Type: transition

Compartments: Golgi membrane

Diseases: influenza



Palmitoylation of influenza A M2 occurs in the ER, or cis golgi network, following tetramerisation. The palmitoylation reaction proceeds via a labile thioester type bond at a specific residue of M2 (Sugrue et al., 1990).

Followed by: Transport of processed viral proteins to the cell membrane

Literature references

Hay, AJ., Belshe, RB., Sugrue, RJ. (1990). Palmitoylation of the influenza A virus M2 protein. *Virology, 179*, 51-6. ↗

Kendal, A., Klenk, HD., Veit, M., Rott, R. (1991). The M2 protein of influenza A virus is acylated. *J Gen Virol, 72*, 1461-5. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Association of HA into rafts ↗

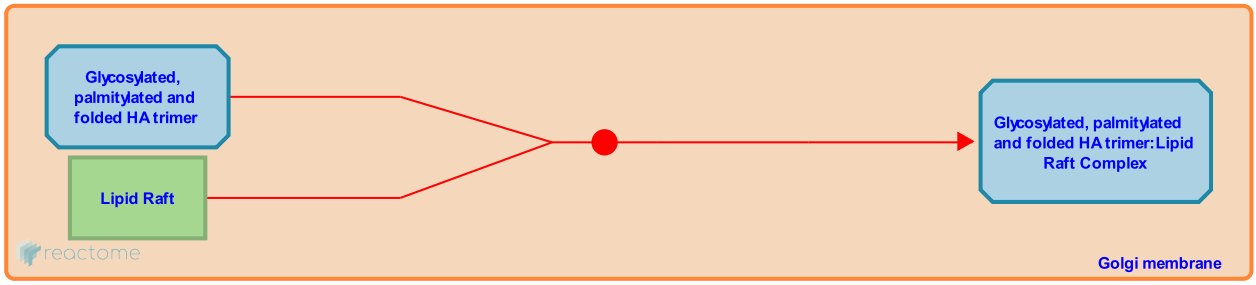
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-168862

Type: binding

Compartments: Golgi membrane

Diseases: influenza



Influenza virus buds preferentially from lipid rafts (Scheiffele et al, 1999). NA protein individually accumulates at, and is selectively incorporated into rafts (Kundu et al., 1996). The signals for raft association lie within the transmembranse domain (TMD), (Barman et al., 2001, Barman et al., 2004), and raft association of NA has been shown to be essential for efficient virus replication. This is believed to be due to a requirement for a concentration of NA at specific areas of the plasma membrane to support a level of NA incorporation into budding particles sufficient to allow for efficient virus release (Barman et al., 2004).

Preceded by: Palmitoylation of cysteine residues on HA in the cis-Golgi network

Followed by: Transport of processed viral proteins to the cell membrane

Literature references

Lamb, RA., Leser, GP., Takeda, M., Russell, CJ. (2003). Influenza virus hemagglutinin concentrates in lipid raft microdomains for efficient viral fusion. *Proc Natl Acad Sci U S A, 100*, 14610-7. ↗

Roth, MG., Scheiffele, P., Simons, K. (1997). Interaction of influenza virus haemagglutinin with sphingolipid-cholesterol membrane domains via its transmembrane domain. *EMBO J, 16*, 5501-8. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Association of NP into rafts ↗

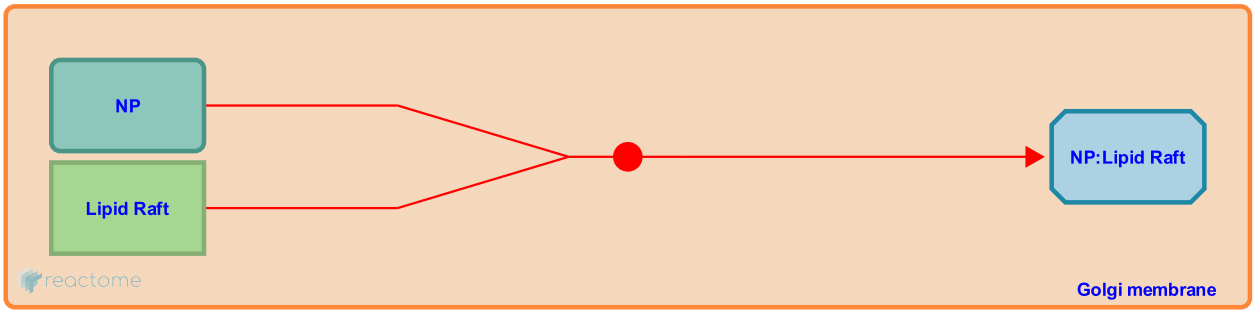
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-168882

Type: binding

Compartments: Golgi membrane

Diseases: influenza



There is evidence that NP alone is intrinsically targeted to the apical plasma membrane and associates with lipid rafts in a cholesterol-dependent manner, which suggests that RNPs could reach the assembly site independently of the other viral components.

Followed by: Transport of processed viral proteins to the cell membrane

Literature references

Amorim, MJ., Digard, P., Carrasco, M. (2004). Lipid raft-dependent targeting of the influenza A virus nucleoprotein to the apical plasma membrane. *Traffic, 5*, 979-92. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Association of NA into rafts ↗

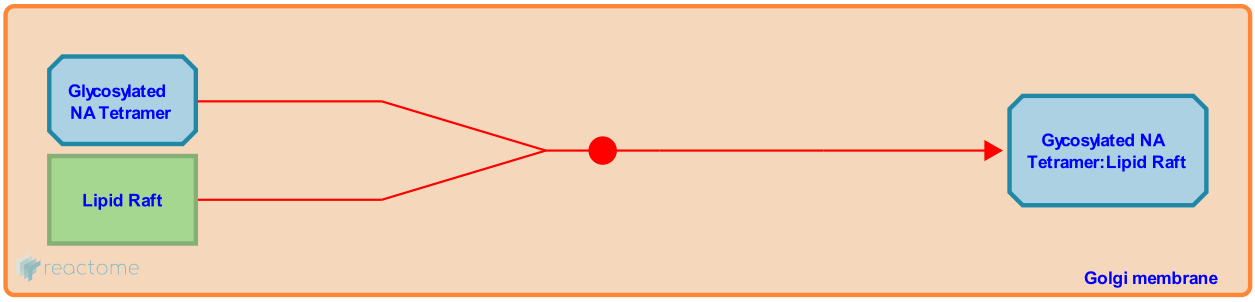
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-195726

Type: binding

Compartments: Golgi membrane

Diseases: influenza



Influenza virus buds preferentially from lipid rafts (Scheiffele et al, 1999). NA protein individually accumulates at, and is selectively incorporated into rafts (Kundu et al., 1996). The signals for raft association lie within the transmembranse domain (TMD), (Barman et al., 2001, Barman et al., 2004), and raft association of NA has been shown to be essential for efficient virus replication. This is believed to be due to a requirement for a concentration of NA at specific areas of the plasma membrane to support a level of NA incorporation into budding particles sufficient to allow for efficient virus release (Barman et al., 2004).

Preceded by: Transport of HA trimer, NA tetramer and M2 tetramer from the endoplasmic reticulum to the Golgi Apparatus

Followed by: Transport of processed viral proteins to the cell membrane

Literature references

Ali, A., Barman, S., Adhikary, L., Nayak, DP., Hui, EK. (2001). Transport of viral proteins to the apical membranes and interaction of matrix protein with glycoproteins in the assembly of influenza viruses. *Virus Res, 77*, 61-9. ↗

Editions

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2007-05-01	Authored	Steel, J.

Transport of processed viral proteins to the cell membrane ↗

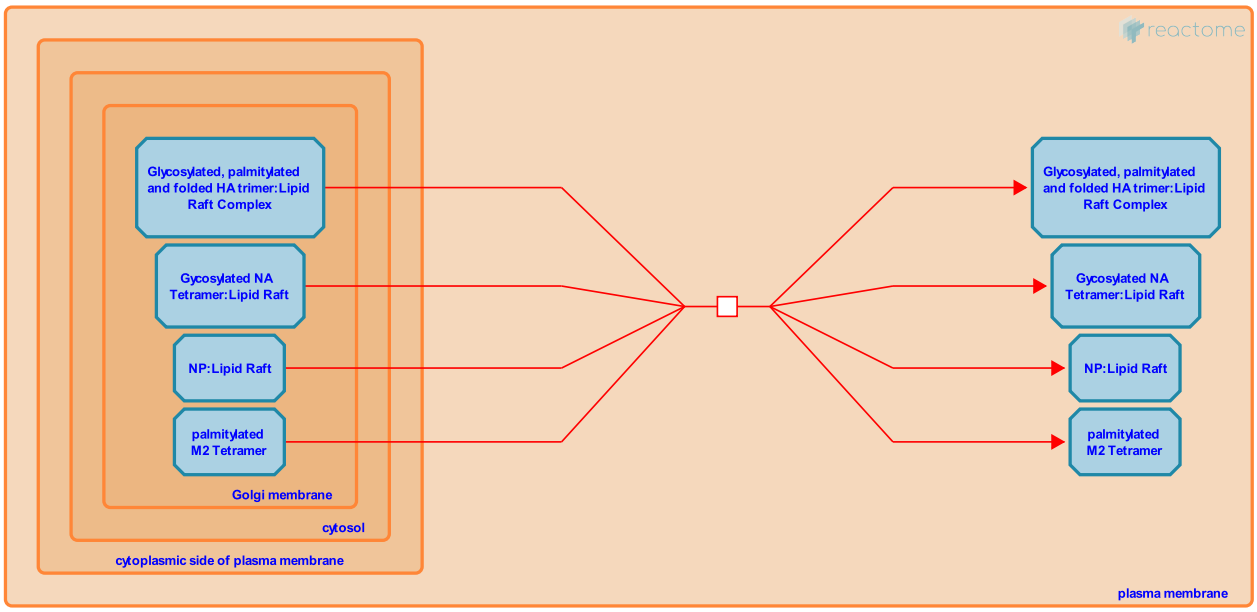
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-195730

Type: transition

Compartments: plasma membrane

Diseases: influenza



Once processed, the viral proteins are transported from the golgi apparatus to the plasma membrane.

Preceded by: Association of NA into rafts, Association of HA into rafts, Palmitoylation of cysteine residues on M2 in the cis-golgi network, Association of NP into rafts

Literature references

Olkkonen, VM., Heino, S., Ikonen, E., Somerharju, P., Ehnholm, C., Lusa, S. (2000). Dissecting the role of the golgi complex and lipid rafts in biosynthetic transport of cholesterol to the cell surface. *Proc Natl Acad Sci U S A, 97*, 8375-80. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

Accumulation of M1 at the inner leaflet of the lipid bilayer ↗

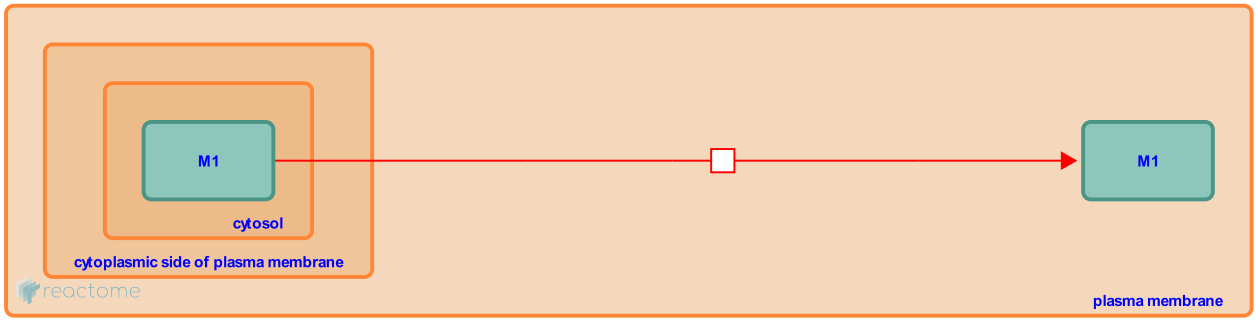
Location: Assembly of Viral Components at the Budding Site

Stable identifier: R-HSA-168894

Type: transition

Compartments: plasma membrane, cytosol

Diseases: influenza



There is evidence for the association of M1 with lipid rafts in influenza infected cells, whereas M1 expressed alone remains soluble (Ali et al., 2000; Zhang and Lamb, 1996), suggesting association of M1 with other viral proteins in targetting to the cell membrane. Coexpression of HA and NA together with M1 has been shown to promote raft association of M1. This association requires the TMD and cytoplasmic tails of HA and NA (Ali et al, 2000; Zhang et al, 2000). This is consistent with M1 becoming associated with HA and NA during their passage through the exocytic pathway to raft domains in the apical membrane. alternatively M1 may use the cytoskeleton to reach the virus assembly site, as M1 interacts with cytoskeletal components (Alvalos et al., 1997). The M1 interaction depends on the presence of RNP and is most likely mediated by direct binding of F-actin by NP (Digard et al., 1999).

Literature references

Lamb, RA., Zhang, J. (1996). Characterization of the membrane association of the influenza virus matrix protein in living cells. *Virology, 225*, 255-66. ↗

Editions

2007-05-01	Reviewed	Rush, MG., Squires, B.
2007-05-01	Authored	Steel, J.

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