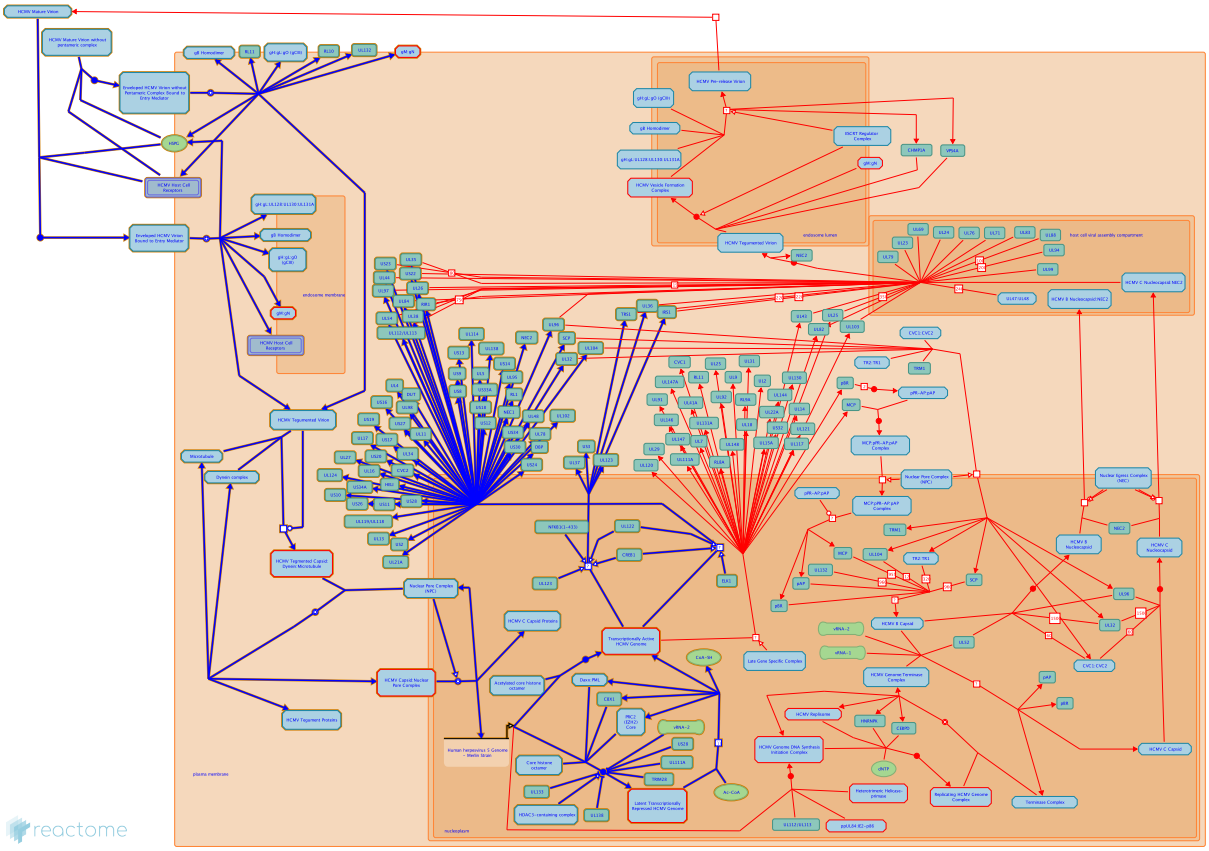
HCMV Early Events



Caposio, P., Gillespie, ME., Streblow, DN.

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

19/09/2021

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. ↗

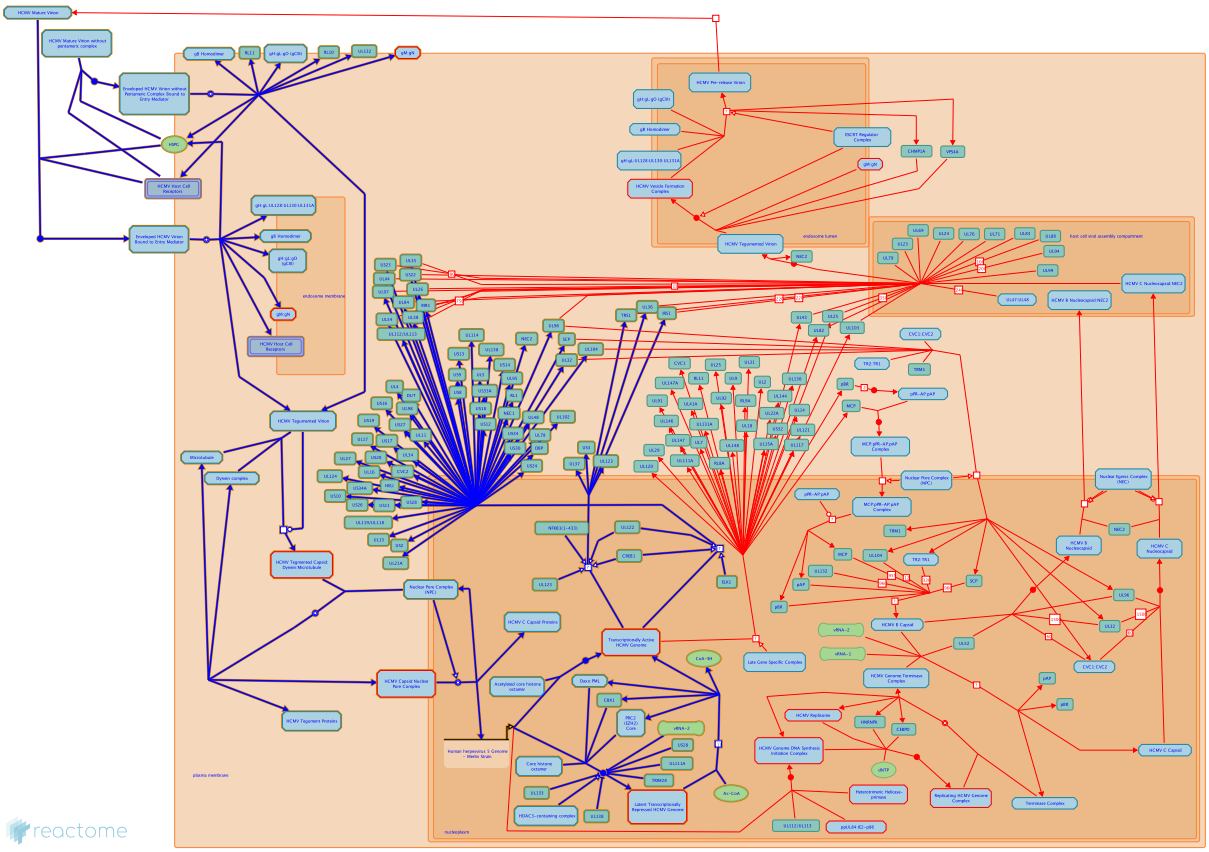
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

HCMV Early Events ↗

Stable identifier: R-HSA-9609690

Diseases: viral infectious disease



Once in the cytoplasm the capsid and tegument proteins are free to interact with host proteins. The capsid travels to the nucleus, where the genome is delivered and circularized. Tegument proteins regulate host cell responses and initiate the expression of viral I immediate early genes. This is followed by the expression of delayed early genes.

Literature references

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins.*

Wilkinson, GW., Davison, AJ., Tomasec, P., Fielding, CA., Aicheler, R., Murrell, I. et al. (2015). Human cytomegalovirus: taking the strain. *Med. Microbiol. Immunol., 204*, 273-84. ↗

Jean Beltran, PM., Cristea, IM. (2014). The life cycle and pathogenesis of human cytomegalovirus infection: lessons from proteomics. *Expert Rev Proteomics, 11*, 697-711. ↗

Schottstedt, V., Blümel, J., Burger, R., Drosten, C., Gröner, A., Gürtler, L. et al. (2010). Human Cytomegalovirus (HCMV) - Revised. *Transfus Med Hemother, 37*, 365-375. ↗

Editions

2018-05-26	Authored	Gillespie, ME.
2019-10-18	Reviewed	Streblow, DN., Caposio, P.

HCMV Binds to the Host Cell via heparan sulfate proteoglycans (HSPG)

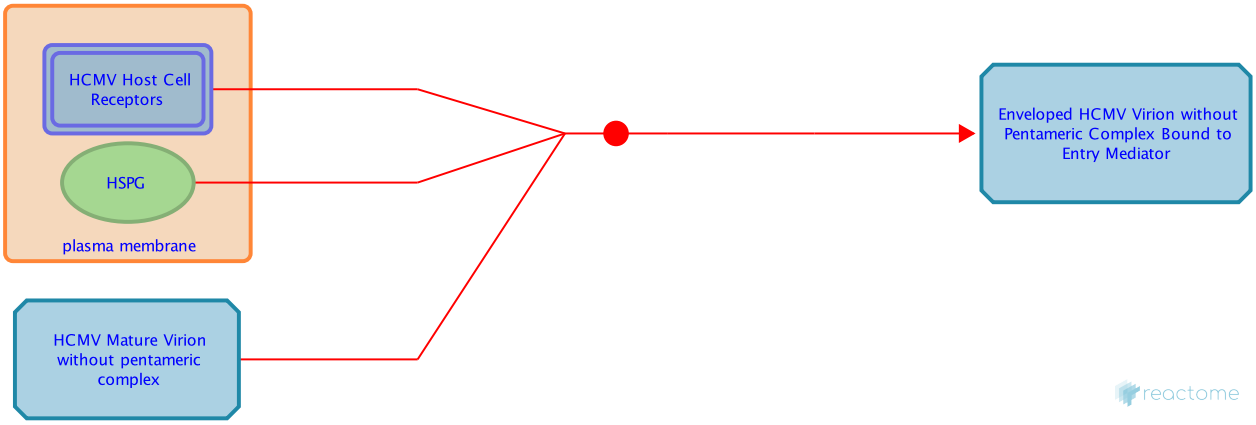
Location: HCMV Early Events

Stable identifier: R-HSA-9609689

Type: binding

Compartments: extracellular region

Diseases: viral infectious disease



Viral attachment and penetration of Human Cytomegalovirus (HCMV) occurs either via direct HCMV fusion with the cell membrane or via endocytosis. The endocytic mechanism occurs with cell types including endothelial and epithelial cells, where the pentameric viral protein complex, gH:gL:p128:p130:p131A, facilitates entry.

Followed by: Fusion of HCMV Envelope with Plasma Membrane

Literature references

Sarrazin, S., Lamanna, WC., Esko, JD. (2011). Heparan sulfate proteoglycans. *Cold Spring Harb Perspect Biol, 3*.

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Spaderna, S., Kropff, B., Ködel, Y., Shen, S., Coley, S., Lu, S. et al. (2005). Deletion of gpUL132, a structural component of human cytomegalovirus, results in impaired virus replication in fibroblasts. *J. Virol., 79*, 11837-47.

Editions

2018-05-30	Authored	Gillespie, ME.
2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Fusion of HCMV Envelope with Plasma Membrane ↗

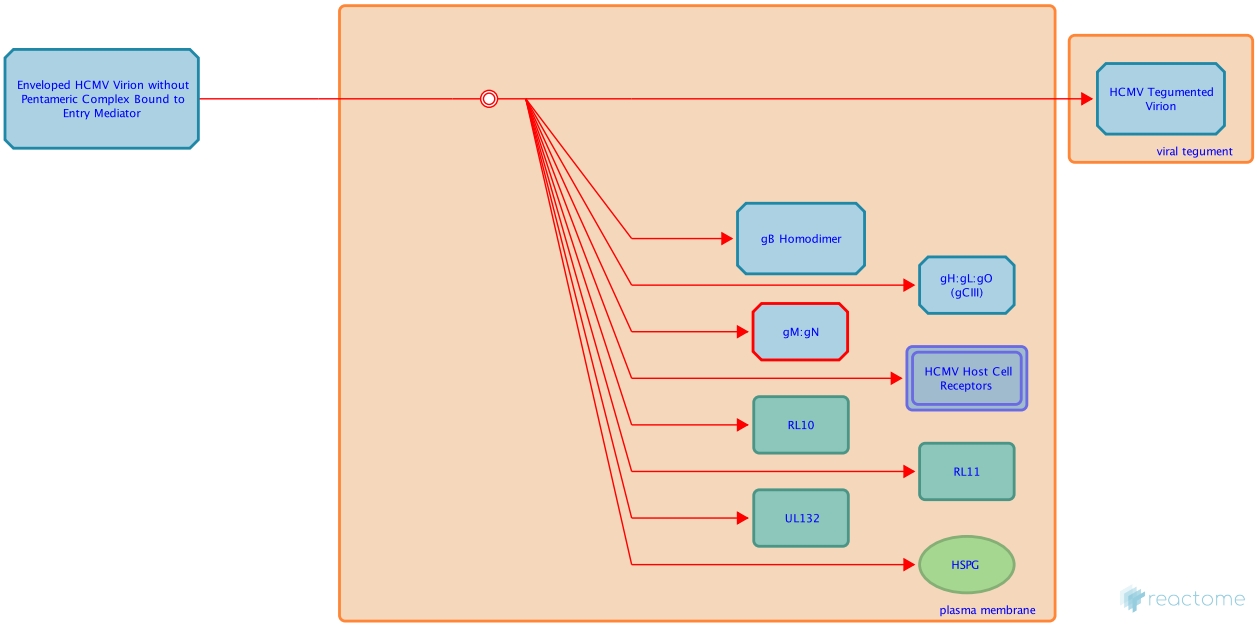
Location: HCMV Early Events

Stable identifier: R-HSA-9611158

Type: dissociation

Compartments: plasma membrane

Diseases: viral infectious disease



Once Human cytomegalovirus (HCMV) initial attachs to cell surface heparan sulfate proteoglycans (HS-PGs), the virus fuses with thecell membrane.

Preceded by: HCMV Binds to the Host Cell via heparan sulfate proteoglycans (HSPG)

Followed by: Viral UL47:UL48 Proteins Bind HCMV Tegumented Virion to Host Microtuble and Dynein complexs

Literature references

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Editions

2018-06-14	Authored	Gillespie, ME.
2019-10-18	Reviewed	Streblow, DN., Caposio, P.

HCMV Binds Host Cell Receptor - Endocytic Pathway ↗

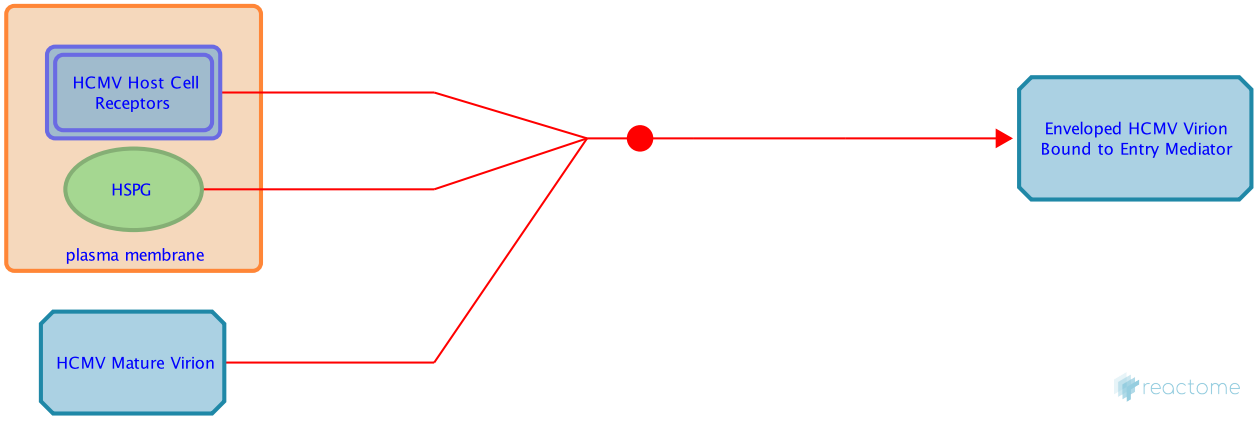
Location: HCMV Early Events

Stable identifier: R-HSA-9610867

Type: binding

Compartments: extracellular region

Diseases: viral infectious disease



Viral attachment and penetration of Human Cytomegalovirus (HCMV) occurs either via direct HCMV fusion with the cell membrane or via endocytosis. The endocytic mechanism occurs with cell types including endothelial and epithelial cells, where the pentameric viral protein complex, gH:gL:p128:p130:p131A, facilitates entry.

Followed by: Endocytic Uptake of HCMV Virion

Literature references

Sarrazin, S., Lamanna, WC., Esko, JD. (2011). Heparan sulfate proteoglycans. *Cold Spring Harb Perspect Biol, 3*. ↗

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Sinzger, C. (2008). Entry route of HCMV into endothelial cells. *J. Clin. Virol., 41*, 174-9. ↗

Gabaev, I., Steinbrück, L., Pokoyski, C., Pich, A., Stanton, RJ., Schwinzer, R. et al. (2011). The human cytomegalovirus UL11 protein interacts with the receptor tyrosine phosphatase CD45, resulting in functional paralysis of T cells . *PLoS Pathog., 7*, e1002432. ↗

Editions

2018-05-30	Authored	Gillespie, ME.
2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Endocytic Uptake of HCMV Virion ↗

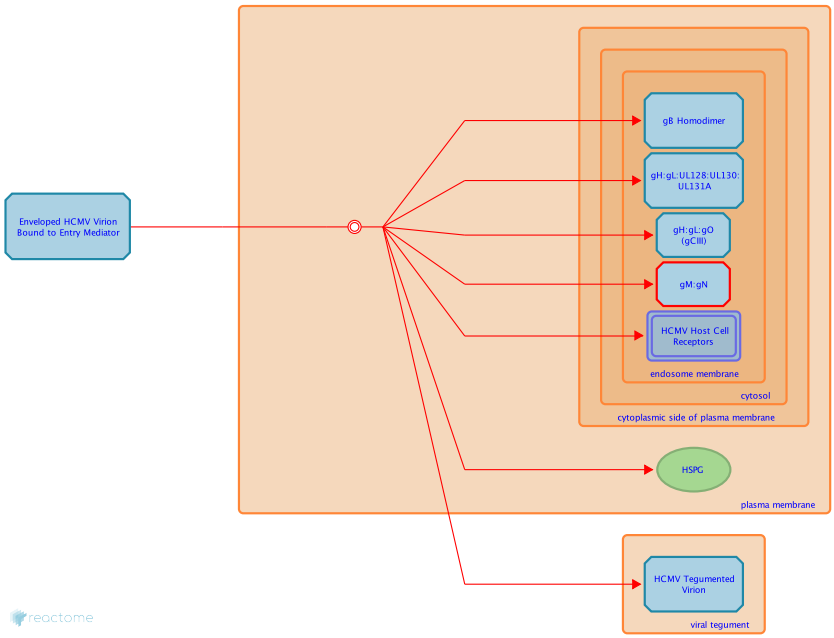
Location: HCMV Early Events

Stable identifier: R-HSA-9611147

Type: dissociation

Compartments: plasma membrane

Diseases: viral infectious disease



Once the pentameric viral protein complex, gH:gL:p128:p130:p131A, facilitates attchment of the Human Cytomegalovirus (HCMV) endocytic uptake allows the virion to enter epithelial and endothelial cells. The virion is released from the endocytic vesicle by low-pH-dependent fusion of the virion coat with endosomes membrane.

Preceded by: HCMV Binds Host Cell Receptor - Endocytic Pathway

Followed by: Viral UL47:UL48 Proteins Bind HCMV Tegumented Virion to Host Microtuble and Dynein complexs

Literature references

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Editions

2018-06-14	Authored	Gillespie, ME.
2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Viral UL47:UL48 Proteins Bind HCMV Tegumented Virion to Host Microtuble and Dynein complexs ↗

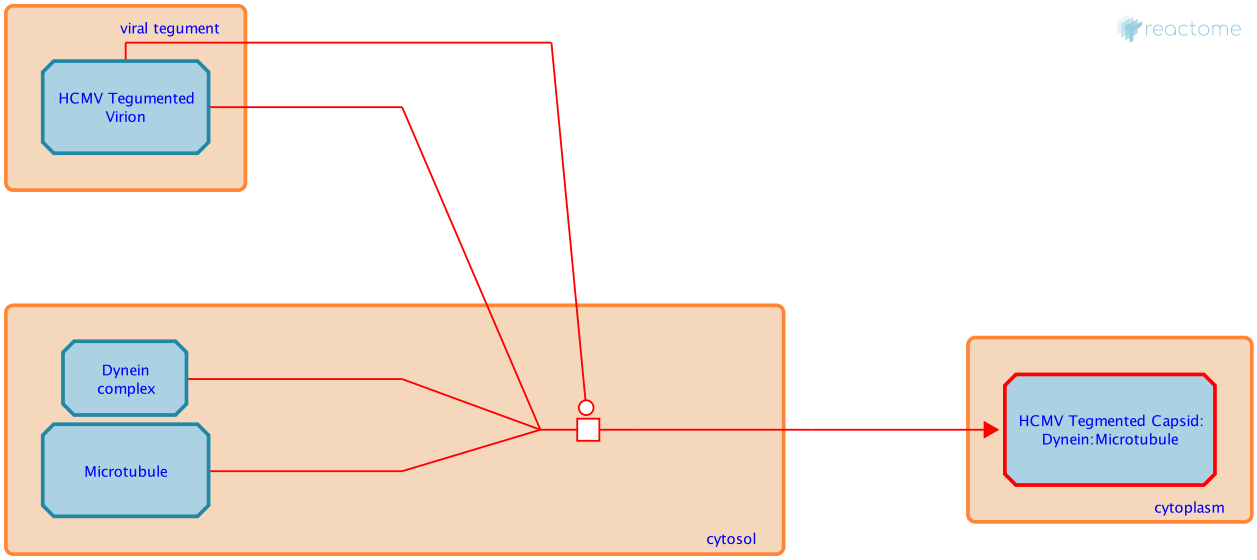
Location: HCMV Early Events

Stable identifier: R-HSA-9614343

Type: transition

Compartments: cytosol

Diseases: viral infectious disease



Tegument proteins help deliver the Human Cytomegalovirus (HCMV) genome-containing capsid to the nucleus during the viral entry process. Signals initiated upon receptor binding induce cellular antiviral responses but may also prime the cell for subsequent events during viral entry. The Capsid-associated tegument proteins UL47 and UL48 (and perhaps pp150) direct capsids along microtubules (MTs) toward nuclear pore complexes driven by cellular motor proteins such as dynein.

Preceded by: Endocytic Uptake of HCMV Virion, Fusion of HCMV Envelope with Plasma Membrane

Followed by: HCMV Nuclear Pore Docking

Literature references

Ogawa-Goto, K., Tanaka, K., Gibson, W., Moriishi, E., Miura, Y., Kurata, T. et al. (2003). Microtubule network facilitates nuclear targeting of human cytomegalovirus capsid. *J. Virol., 77*, 8541-7. ↗

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Sinzger, C. (2008). Entry route of HCMV into endothelial cells. *J. Clin. Virol., 41*, 174-9. ↗

Editions

2018-06-20	Authored	Gillespie, ME.
2019-10-18	Reviewed	Streblow, DN., Caposio, P.

HCMV Nuclear Pore Docking ↗

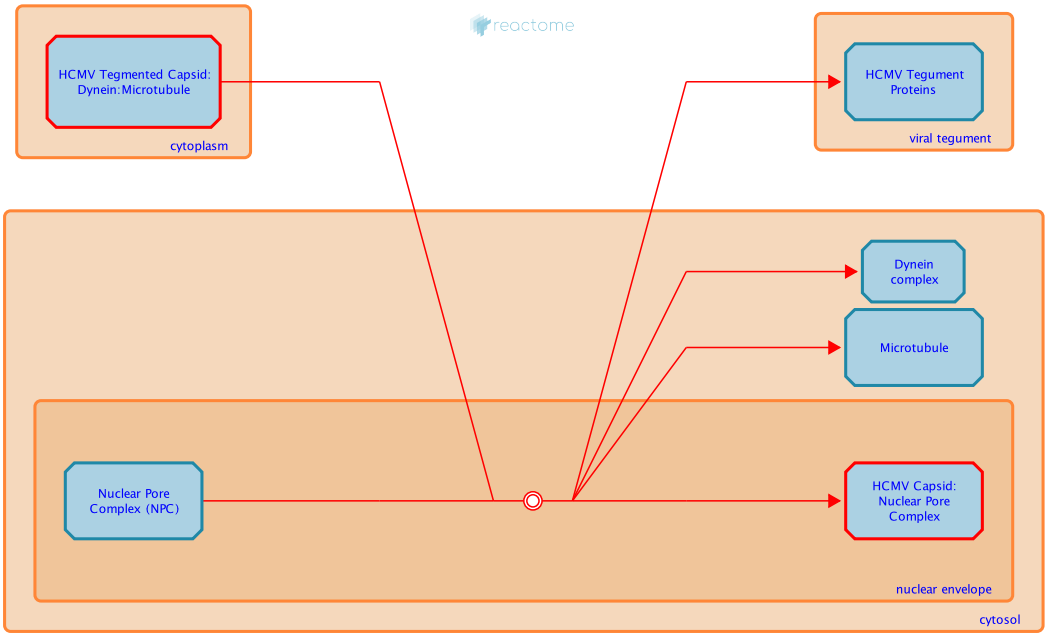
Location: HCMV Early Events

Stable identifier: R-HSA-9614367

Type: dissociation

Compartments: nuclear envelope

Diseases: viral infectious disease



Virion capsids eventually dissociate from microtubules, dock at nuclear pores, and release their DNA into the nucleus. The role of tegument proteins in this process is implicated but has not been described in detail.

Preceded by: Viral UL47:UL48 Proteins Bind HCMV Tegumented Virion to Host Microtuble and Dynein complexs

Followed by: Transport of HCMV DNA Into the Nucleus

Literature references

Kalejta, RF. (2008). Tegument proteins of human cytomegalovirus. *Microbiol. Mol. Biol. Rev., 72*, 249-65, table of contents. ↗

Editions

2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Transport of HCMV DNA Into the Nucleus ↗

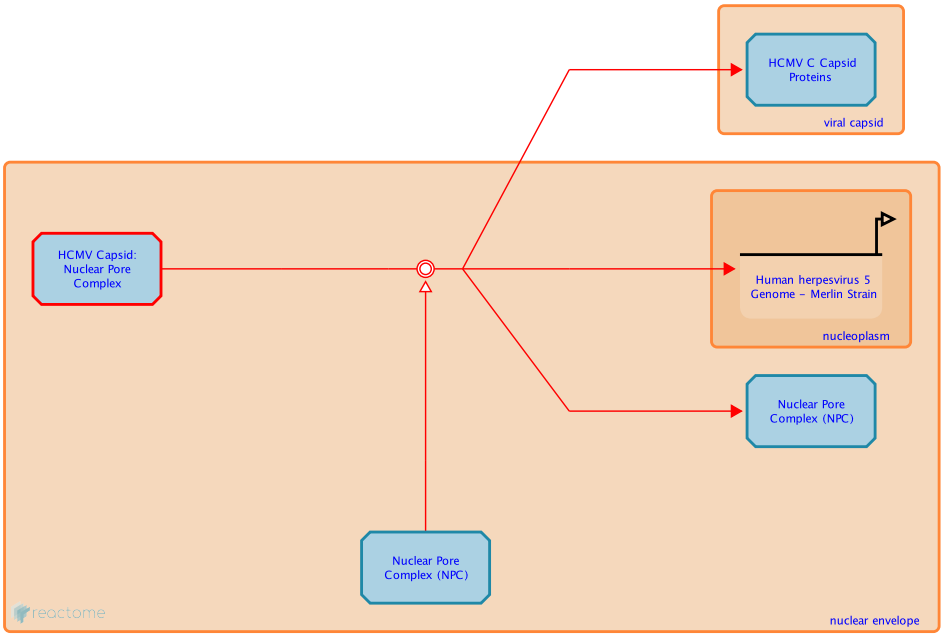
Location: HCMV Early Events

Stable identifier: R-HSA-9614369

Type: dissociation

Compartments: nuclear envelope

Diseases: viral infectious disease



After the Human Cytomegalovirus (HCMV) capsid docks at the nuclear pore complex the HCMV genome containing capsid is transported into the nucleus.

Preceded by: HCMV Nuclear Pore Docking

Followed by: Transcriptional Activation of the HCMV Genome, Latent Transcriptionally Repressed HCMV Genome

Literature references

Kalejta, RF. (2008). Tegument proteins of human cytomegalovirus. *Microbiol. Mol. Biol. Rev., 72*, 249-65, table of contents. ↗

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Editions

2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Transcriptional Activation of the HCMV Genome ↗

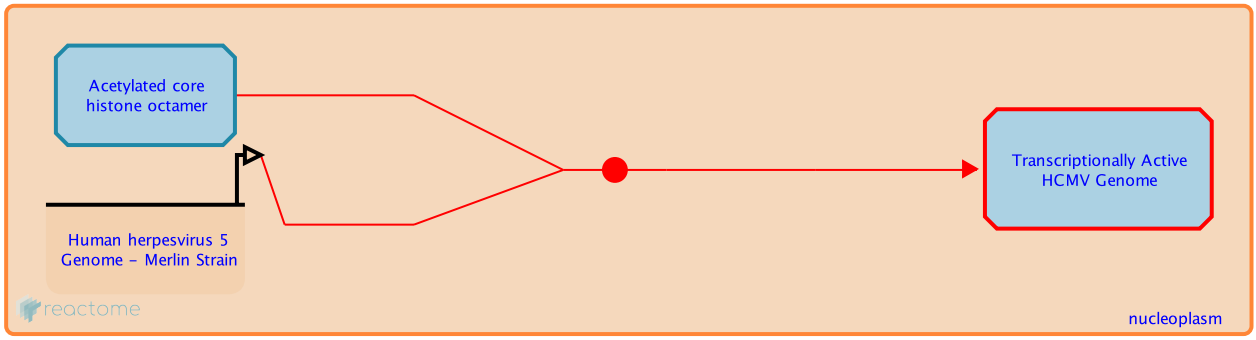
Location: HCMV Early Events

Stable identifier: R-HSA-9614811

Type: binding

Compartments: nucleoplasm

Diseases: viral infectious disease



Cells infected by with the human cytomegalovirus (HCMV) have two potential fates once the HCMV genome enters the nucleus. In an active infection there is extensive viral gene expression, viral DNA replication and release of progeny virus. In contrast, in a latent infection the lytic transcription programme of HCMV is effectively suppressed and the cells undergo latent infection. The suppression of viral lytic gene expression observed during latency is the result from the cells inability to support robust viral immediate early (IE) gene expression; crucial genes responsible for driving the lytic cycle. The repression of IE gene expression results from specific post-translational modifications of histones associated with the viral major immediate early promoter (MIEP). The histone modifications present on the MIEP impart a repressive chromatin structure preventing transcriptional activity.

Preceded by: Transport of HCMV DNA Into the Nucleus, Activation of Latent HCMV Genome

Followed by: Delayed Early (DE) Gene Expression, Immediate Early (IE) Gene Expression

Literature references

Sinclair, J. (2010). Chromatin structure regulates human cytomegalovirus gene expression during latency, reactivation and lytic infection. *Biochim. Biophys. Acta, 1799*, 286-95. ↗

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Goodrum, F. (2016). Human Cytomegalovirus Latency: Approaching the Gordian Knot. *Annu Rev Virol, 3*, 333-357. ↗

Dupont, L., Reeves, MB. (2016). Cytomegalovirus latency and reactivation: recent insights into an age old problem. *Rev. Med. Virol., 26*, 75-89. ↗

Elder, E., Sinclair, J. (2019). HCMV latency: what regulates the regulators?. *Med. Microbiol. Immunol.*. ↗

Editions

2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Latent Transcriptinally Repressed HCMV Genome ↗

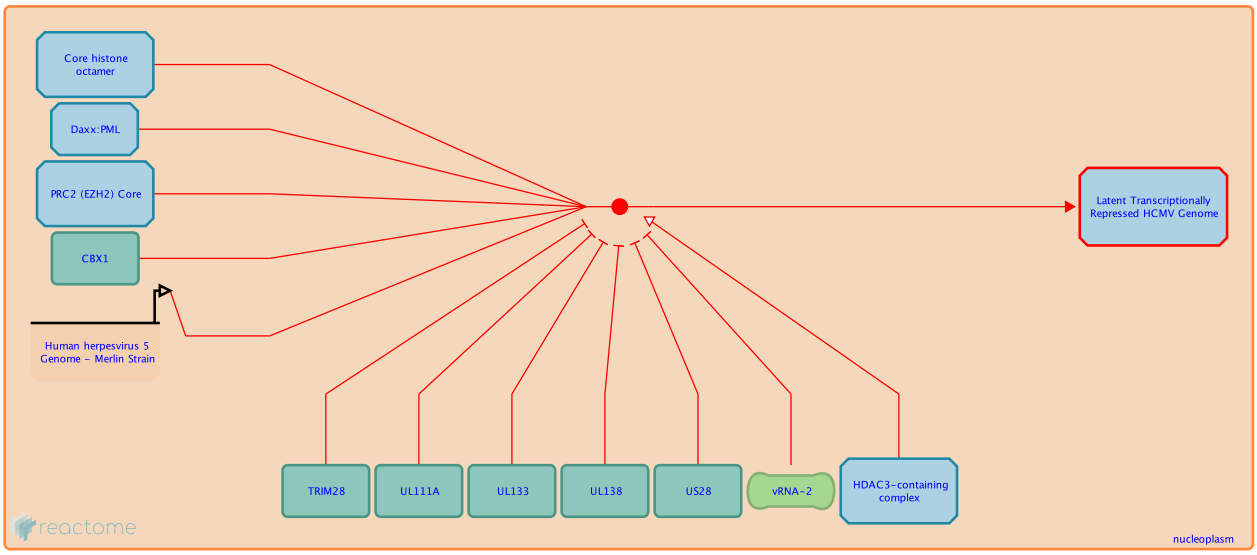
Location: HCMV Early Events

Stable identifier: R-HSA-9614816

Type: binding

Compartments: nucleoplasm

Diseases: viral infectious disease



Cells infected by with the Human Cytomegalovirus (HCMV) have two potential fates once the HCMV genome enters the nucleus. In contrast, in a latent infection the lytic transcription programme of HCMV is effectively suppressed and the cells undergo latent infection. The suppression of viral lytic gene expression observed during latency is the result from the cells inability to support robust viral immediate early (IE) gene expression; crucial genes responsible for driving the lytic cycle. The repression of IE gene expression results from specific post-translational modifications of histones associated with the viral major immediate early promoter (MIEP). The histone modifications present on the MIEP impart a repressive chromatin structure preventing transcriptional activity.

In an active infection there is extensive viral gene expression, viral DNA replication and release of progeny virus.

Preceded by: Transport of HCMV DNA Into the Nucleus

Followed by: Activation of Latent HCMV Genome

Literature references

Sinclair, J. (2010). Chromatin structure regulates human cytomegalovirus gene expression during latency, reactivation and lytic infection. *Biochim. Biophys. Acta, 1799*, 286-95. ↗

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins.*

Goodrum, F. (2016). Human Cytomegalovirus Latency: Approaching the Gordian Knot. *Annu Rev Virol, 3*, 333-357. ↗

Dupont, L., Reeves, MB. (2016). Cytomegalovirus latency and reactivation: recent insights into an age old problem. *Rev. Med. Virol., 26*, 75-89. ↗

Diggins, NL., Hancock, MH. (2018). HCMV miRNA Targets Reveal Important Cellular Pathways for Viral Replication, Latency, and Reactivation. *Noncoding RNA, 4*. ↗

Editions

2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Activation of Latent HCMV Genome ↗

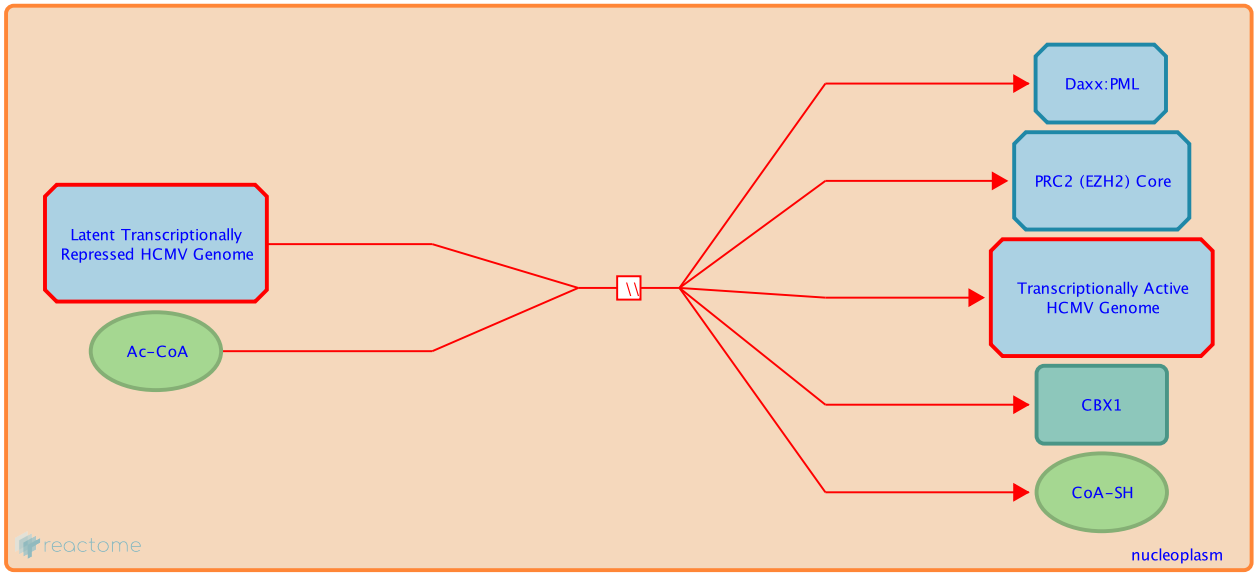
Location: HCMV Early Events

Stable identifier: R-HSA-9614810

Type: omitted

Compartments: nucleoplasm

Diseases: viral infectious disease



A cell containing a repressed or latent Human Cytomegalovirus (HCMV) genome sits quietly carrying on its normal cellular functions. The HCMV silenced HCMV geneome can be activated by a number of cellular events or state changes. Reactivation of HCMV lytic infection is correlated to changes in histone modifications around the MIEP promoter resulting in a new chromatin structure conducive to transcriptional activity. These changes are intimately linked with cell differentiation, a phenomenon known to reactivate latent virus in vivo.

Preceded by: Latent Transcriptinally Repressed HCMV Genome

Followed by: Transcriptional Activation of the HCMV Genome

Literature references

Sinclair, J. (2010). Chromatin structure regulates human cytomegalovirus gene expression during latency, reactivation and lytic infection. *Biochim. Biophys. Acta, 1799*, 286-95. ↗

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Editions

2018-07-25	Authored	Gillespie, ME.
2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Immediate Early (IE) Gene Expression ↗

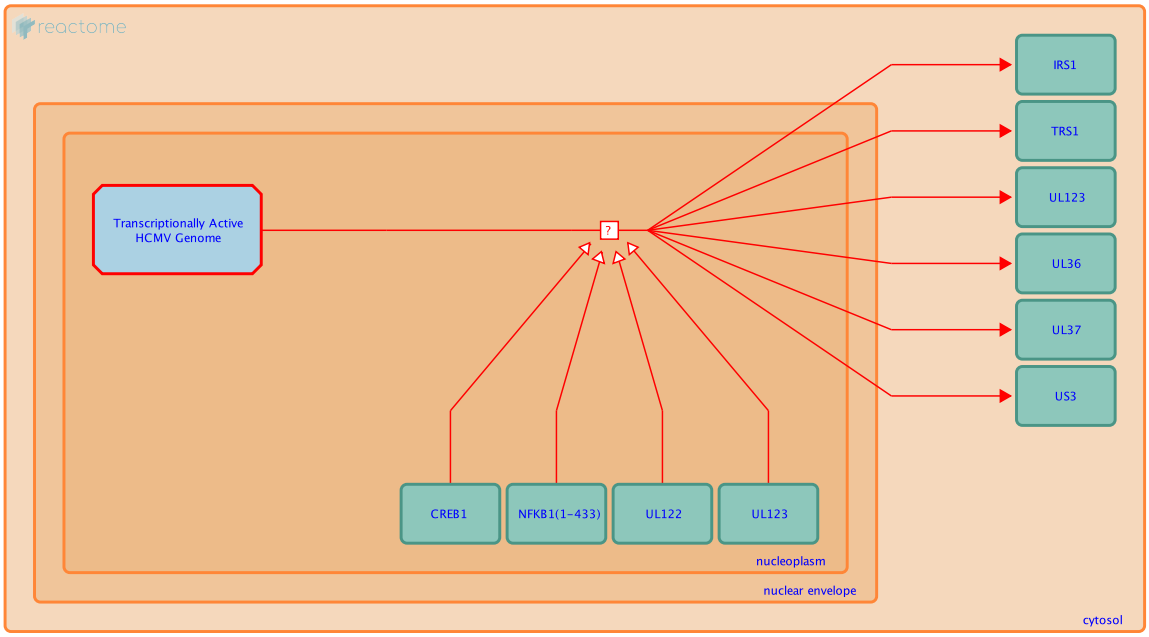
Location: HCMV Early Events

Stable identifier: R-HSA-9621073

Type: uncertain

Compartments: nucleoplasm

Diseases: disease by infectious agent



Once the HCMV genome is delivered to the nucleus, IE gene expression ensues. RNA pol II transcription machinery transcribes IE as well as all other protein-coding and noncoding RNAs made from the HCMV genome. Regulation of viral gene expression occurs via two broad strategies: (1) viral as well as cellular factors that directly influence the transcription machinery by binding to promoter/enhancer elements directly (transcription factors) or through interactions with other proteins (adaptors) (2) viral factors that alter chromatin remodeling by regulating the opposing activities of histone acetyl transferases (HATs) acting together with demethylases and histone deacetylases (HDACs) and methylases. HDAC-dependent repression of viral IE gene expression, in particular, is a cell-intrinsic host defense mechanism that must be defused before productive replication can ensue. Epigenetic regulation is important in permissive cells, even though the viral genome does not take on a recognizable chromatin structure, and also during latency, where viral genomes take on an organized chromatin arrangement and viral HDAC inhibitors can drive reactivation.

Preceded by: Transcriptional Activation of the HCMV Genome

Literature references

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins*.

Editions

2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Delayed Early (DE) Gene Expression ↗

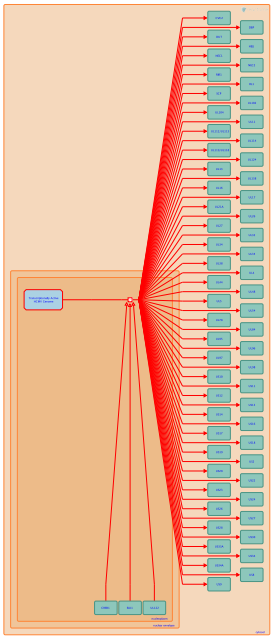
Location: HCMV Early Events

Stable identifier: R-HSA-9623096

Type: uncertain

Compartments: nucleoplasm

Diseases: disease by infectious agent



Following peak expression of major immediate early (MIE) regulatory proteins, the second class of early genes, delayed early (DE), become transcriptionally active independent of the host cell type. Although some DE gene products are produced in abundance from the start, most of the proteins and assorted miRNAs accumulate gradually. The DE period of viral replication continues until viral DNA synthesis initiates. DE genes are crucial for viral DNA synthesis and include several functions that become important later in infection for maturation and egress. Many DE genes have a substantial impact on replication when disrupted. DE gene products dispensable for replication in fibroblasts may contribute to modulation of the host cell and host animal response to infection. Several HCMV DE genes switch or add transcriptional start sites later in infection, which means that transcript levels represent the combined products of different kinetic classes of gene expression.

Preceded by: Transcriptional Activation of the HCMV Genome

Literature references

Knipe, DM., Howley, PM. (2013). Chapter 62 - Cytomegaloviruses, Fields Virology. *Lippincott Williams & Wilkins.*

Editions

2019-10-18	Reviewed	Streblow, DN., Caposio, P.

Table of Contents