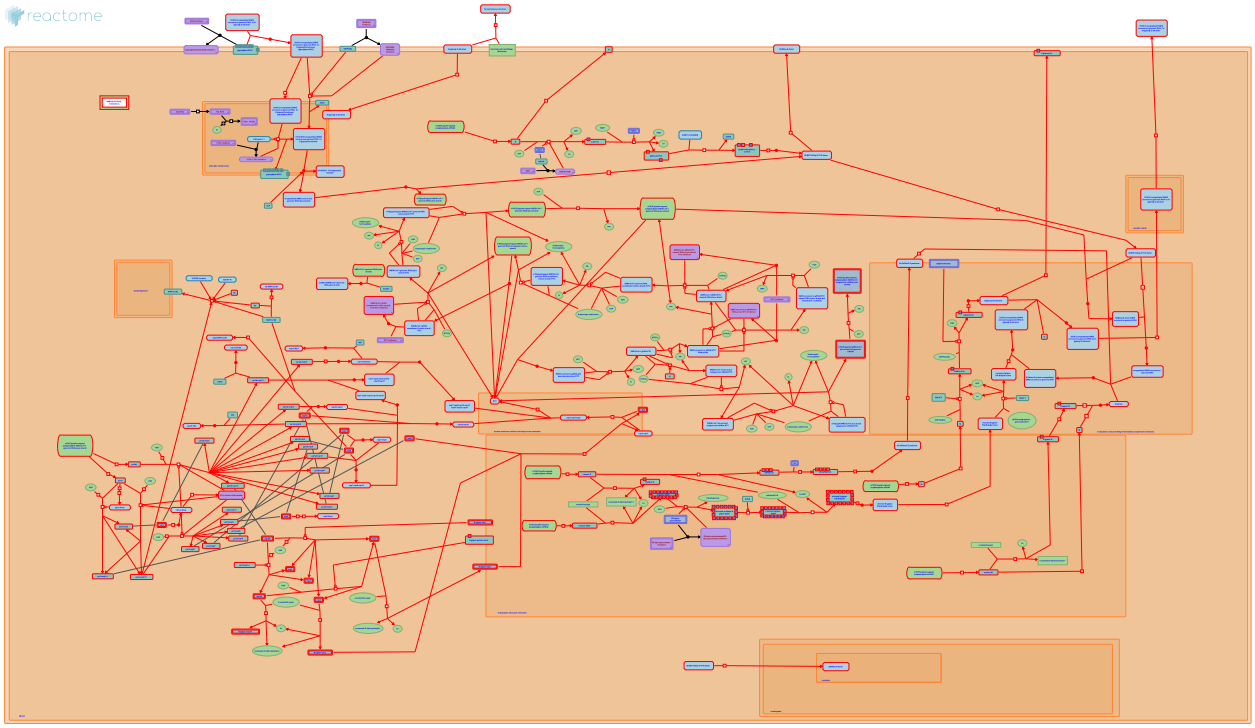
SARS-CoV-1 Infection



Acencio, ML., D'Eustachio, P., Gillespie, ME., Mazein, A., Orlic-Milacic, M., Rothfels, K., Shamovsky, V., Stephan, R.

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

19/09/2024

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. ↗

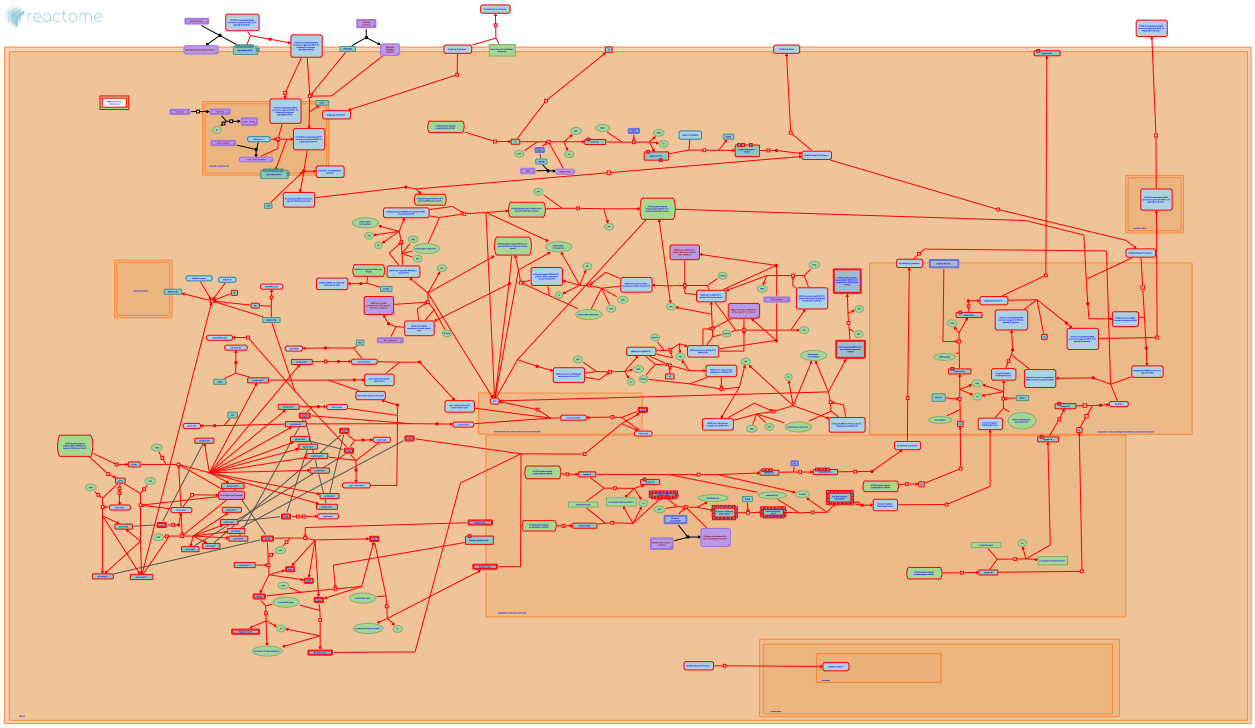
Reactome database release: 89

This document contains 7 pathways (see Table of Contents)

SARS-CoV-1 Infection ↗

Stable identifier: R-HSA-9678108

Diseases: severe acute respiratory syndrome



The SARS-CoV-1 coronavirus is the causative agent of the outbreak of severe acute respiratory syndrome in 2003 that caused 8,098 known cases of the disease and 774 deaths. The molecular events involved in viral infection and the response of the human host to it have since been studied in detail and are annotated here (de Wit et al. 2016; Marra et al. 2003). The SARS-CoV-1 viral infection pathway here uses entries listed in the UniProt "Human SARS coronavirus (SARS-CoV) (Severe acute respiratory syndrome coronavirus)" taxonomy.

SARS-CoV-1 infection begins with the binding of viral S (spike) protein to cell surface angiotensin converting enzyme 2 (ACE2) and endocytosis of the bound virion. Within the endocytic vesicle, host proteases mediate cleavage of S protein into S1 and S2 fragments, leading to S2-mediated fusion of the viral and host endosome membranes and release of the viral capsid into the host cell cytosol. The capsid is uncoated to free the viral genomic RNA, whose cap-dependent translation produces polyprotein pp1a and, by means of a 1-base frameshift, polyprotein pp1ab. Autoproteolytic cleavage of pp1a and pp1ab generates 15 or 16 nonstructural proteins (nsps) with various functions. Importantly, the RNA dependent RNA polymerase (RdRP) activity is encoded in nsp12. Nsp3, 4, and 6 induce rearrangement of the cellular endoplasmic reticulum membrane to form cytosolic double membrane vesicles (DMVs) where the viral replication transcription complex is assembled and anchored. With viral genomic RNA as a template, viral replicase-transcriptase synthesizes a full length negative sense antigenome, which in turn serves as a template for the synthesis of new genomic RNA. The replicase-transcriptase can also switch template during discontinuous transcription of the genome at transcription regulated sequences to produce a nested set of negative-sense subgenomic (sg) RNAs, which are used as templates for the synthesis of positive-sense sgRNAs that are translated to generate viral proteins. Finally, viral particle assembly occurs in the ER Golgi intermediate compartment (ERGIC). Viral M protein provides the scaffold for virion morphogenesis (Fung & Liu 2019; Masters 2006).

Literature references

Artsob, H., Jones, S., Flick, R., Fernando, L., Smailus, DE., Cloutier, A. et al. (2003). The Genome sequence of the SARS-associated coronavirus. *Science, 300*, 1399-404. ↗

Fung, TS., Liu, DX. (2019). Human Coronavirus: Host-Pathogen Interaction. *Annu. Rev. Microbiol., 73*, 529-557. ↗

Editions

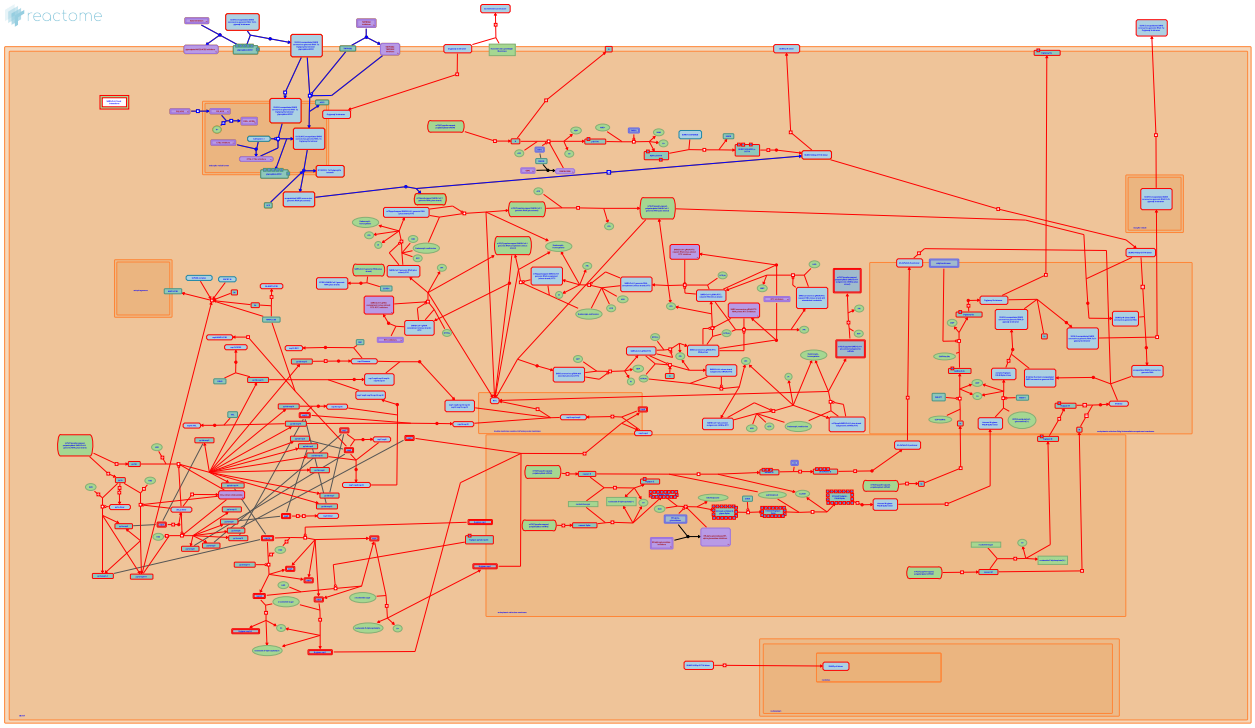
2020-03-24	Authored	Gillespie, ME.
2020-05-21	Edited	D'Eustachio, P.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

Attachment and Entry ↗

Location: SARS-CoV-1 Infection

Stable identifier: R-HSA-9678110

Diseases: severe acute respiratory syndrome



Coronavirus replication is initiated by the binding of S protein to the cell surface receptor(s). The S protein is composed of two functional domains, S1 (bulb) which mediates receptor binding and S2 (stalk) which mediates membrane fusion. Specific interaction between S1 and the cognate receptor triggers a drastic conformational change in S2, leading to fusion between the virus envelope and the cellular membrane and release of the viral nucleocapsid into the host cell cytosol. Receptor binding is the major determinant of the host range and tissue tropism for a coronavirus. Some human coronaviruses (HCoVs) have adopted cell surface enzymes as receptors, angiotensin converting enzyme 2 (ACE2) for SARS-CoV-1 and HCoV NL63. The receptor-bound S protein is activated by cleavage into S1 and S2, mediated by one of two of two host proteases, the endosomal cysteine protease cathepsin L and another trypsin like serine protease. Type II transmembrane serine proteases TMPRSS2 and TMPRSS11D have also been implicated in the activation of S protein of SARS-CoV-1. Host factors may play additional roles in viral entry (not annotated here). Valosin containing protein (VCP) contributes by a poorly understood mechanism to the release of coronavirus from early endosomes. Host factors may also restrict the attachment and entry of HCoV. Some interferon inducible transmembrane proteins (IFITMs) exhibited broad spectrum antiviral functions against various RNA viruses including SARS-CoV-1 while others may facilitate HCoV entry into host cells (Fung & Liu 2019).

Literature references

Fung, TS., Liu, DX. (2019). Human Coronavirus: Host-Pathogen Interaction. *Annu. Rev. Microbiol., 73,* 529-557. ↗

Editions

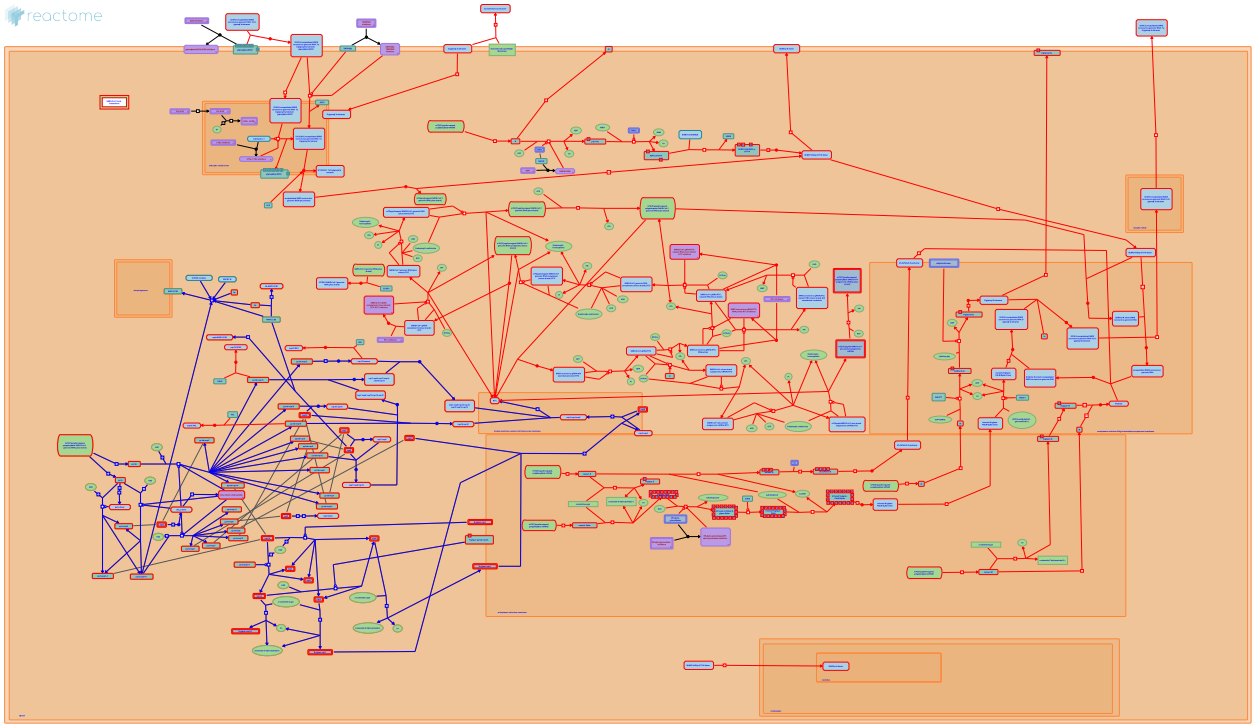
2020-03-24	Authored	Gillespie, ME.
2020-05-21	Edited	D'Eustachio, P.
2020-05-26	Edited	Gillespie, ME.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

Translation of Replicase and Assembly of the Replication Transcription Complex ↗

Location: SARS-CoV-1 Infection

Stable identifier: R-HSA-9679504

Diseases: severe acute respiratory syndrome



After entry and uncoating, the SARS-CoV-1 genomic RNA serves as a transcript to allow cap dependent translation of ORF1a to produce polyprotein pp1a. A slippery sequence and an RNA pseudoknot near the end of ORF1a enable 25 - 30% of the ribosomes to undergo -1 frameshifting, to continue translation of ORF1b to produce a longer polyprotein pp1ab. The autoproteolytic cleavage of pp1a and pp1ab generates 15-16 nonstructural proteins (nsps) with various functions. The RNA dependent RNA polymerase (RdRP) activity is encoded in nsp12, and papain like protease (PLPro) and main protease (Mpro) activities are encoded in nsp3 and nsp5, respectively. nsp3, 4, and 6 induce rearrangement of the cellular membrane to form double membrane vesicles (DMVs) where the coronavirus replication transcription complex (RTC) is assembled and anchored.

Programmed ribosomal frameshifting (PRF) may be regulated by viral or host factors in addition to viral RNA secondary structures. For example, PRF in the related arterivirus porcine reproductive and respiratory syndrome virus (PRRSV) is transactivated by the viral protein nsp1, which interacts with the PRF signal via a putative RNA binding motif. A host RNA-binding protein called annexin A2 (ANXA2) binds the pseudoknot structure in the IBV genome. Host factors in the early secretory pathway appear to be involved in DMV formation and RTC assembly: Golgi specific brefeldin A resistance guanine nucleotide exchange factor 1 (GBF1) and its effector ADP ribosylation factor 1 (ARF1) are both required for normal DMV formation and efficient RNA replication of mouse hepatitis virus (MHV), a prototypic betacoronavirus that infects mice (Fung & Liu 2019).

Literature references

Fung, TS., Liu, DX. (2019). Human Coronavirus: Host-Pathogen Interaction. *Annu. Rev. Microbiol., 73*, 529-557. ↗

Editions

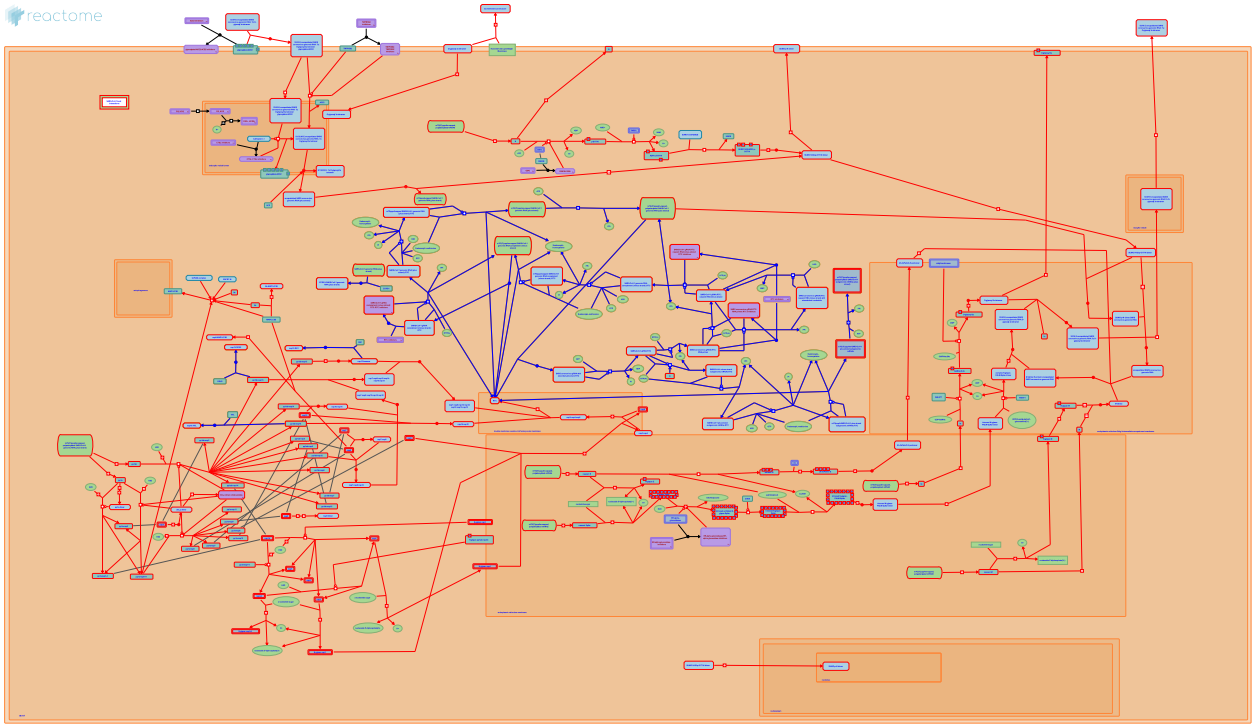
2020-05-15	Authored	Stephan, R.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

SARS-CoV-1 Genome Replication and Transcription ↗

Location: SARS-CoV-1 Infection

Stable identifier: R-HSA-9679514

Diseases: severe acute respiratory syndrome



Using the genomic RNA as a template, the coronavirus replicase synthesizes full-length negative-sense antigenome, which in turn serves as a template for the synthesis of new genomic RNA (Masters 2006). The polymerase can also switch template during discontinuous transcription of the genome at specific sites called transcription-regulated sequences, thereby producing a 5'-nested set of negative-sense sgRNAs, which are used as templates for the synthesis of a 3'-nested set of positive-sense sgRNAs (Masters 2006). Although genome replication/transcription is mainly mediated by the viral replicase and confines in the replication-transcription complex (RTC), the involvement of various additional viral and host factors has been implicated. For instance, coronavirus N protein is known to serve as an RNA chaperone and facilitate template switching (Zúñiga et al. 2007, Zúñiga et al. 2010). Importantly, the N protein of SARS-CoV-1 and mouse hepatitis virus (MHV-JHM) is also phosphorylated by the host glycogen synthase kinase 3 (GSK3), and inhibition of GSK3 was shown to inhibit viral replication in Vero E6 cells infected with SARS-CoV-1 (Wu et al. 2009). Additionally, GSK3-mediated phosphorylation of the MHV-JHM N protein recruited an RNA-binding protein DEAD-box helicase 1 (DDX1), which facilitates template read-through, favoring the synthesis of genomic RNA and longer sgRNAs (Wu et al. 2014). Another RNA-binding protein called heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) can also bind tightly to SARS-CoV N protein and potentially regulate viral RNA synthesis (Luo et al. 2005). Host RNA-binding proteins could also bind directly to untranslated regions (UTRs) of the coronavirus genome to modulate replication/transcription, such as zinc finger CCHC-type and RNA-binding motif 1 (ZCRB1) binding to the 5-UTR of IBV (Tan et al. 2012), mitochondrial aconitase binding to the 3' UTR of MHV (Nanda and Leibowitz 2001), and poly(A)-binding protein (PABP) to the poly(A) tail of bovine coronavirus (Spagnolo and Hogue 2000). For review, please refer to Snijder et al. 2016 and Fung and Liu 2019.

Literature references

Tan, YW., Hong, W., Liu, DX. (2012). Binding of the 5'-untranslated region of coronavirus RNA to zinc finger CCHC-type and RNA-binding motif 1 enhances viral replication and transcription. *Nucleic Acids Res., 40,* 5065-77. ↗

Spagnolo, JF., Hogue, BG. (2000). Host protein interactions with the 3' end of bovine coronavirus RNA and the requirement of the poly(A) tail for coronavirus defective genome replication. *J. Virol., 74,* 5053-65. ↗

Mateos-Gomez, PA., Enjuanes, L., Palacio, L., Zúñiga, S., Cruz, JL., Sola, I. (2010). Coronavirus nucleocapsid protein facilitates template switching and is required for efficient transcription. *J. Virol., 84,* 2169-75. ↗

Leibowitz, JL., Nanda, SK. (2001). Mitochondrial aconitase binds to the 3'-UTR of mouse hepatitis virus RNA. *Adv. Exp. Med. Biol., 494*, 603-8. ↗

Shen, X., Chen, Q., Luo, H., Jiang, H., Chen, K., Chen, J. (2005). The nucleocapsid protein of SARS coronavirus has a high binding affinity to the human cellular heterogeneous nuclear ribonucleoprotein A1. *FEBS Lett., 579*, 2623-8. ↗

Editions

2020-05-27	Reviewed	Mazein, A., Acencio, ML.
2020-05-27	Authored	Orlic-Milacic, M.

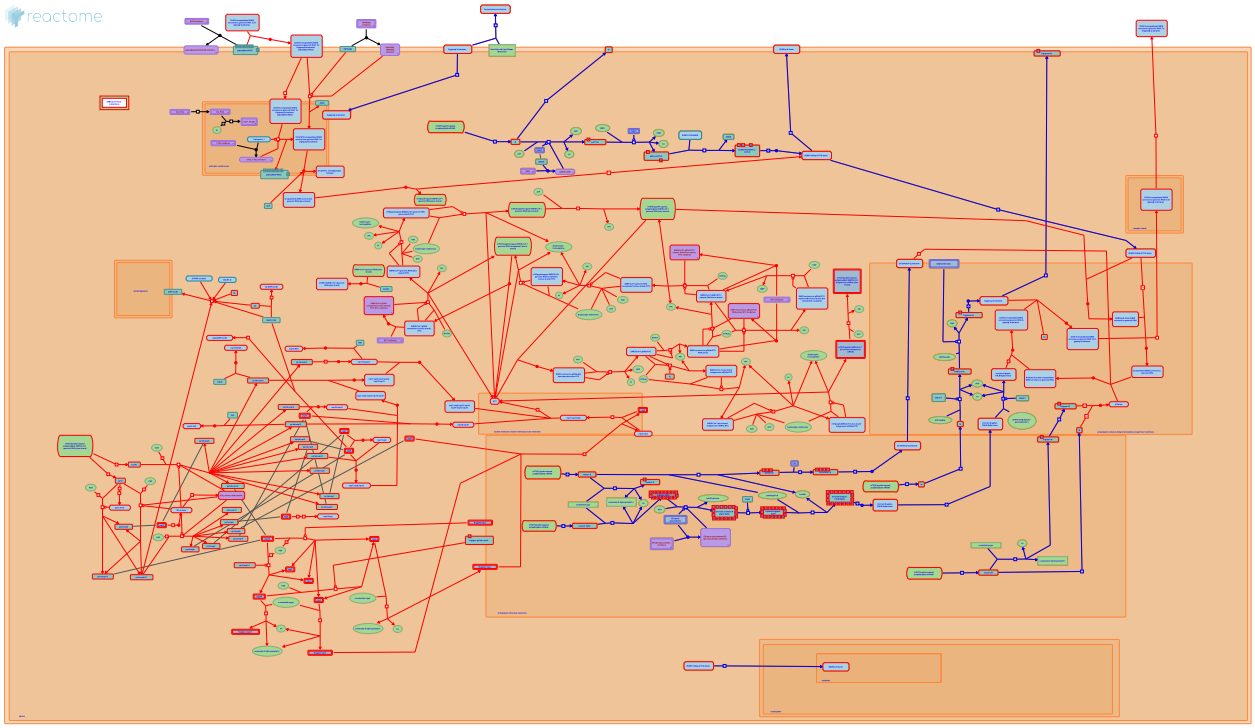
Translation of Structural Proteins ↗

Location: SARS-CoV-1 Infection

Stable identifier: R-HSA-9683701

Compartments: endoplasmic reticulum lumen, cytosol

Diseases: severe acute respiratory syndrome



SARS-CoV-1 mRNA is translated according to the ribosomal scanning model. Virus mRNA is capped and polyadenylated, with regions of nontranslated sequences on both the 5' and 3' ends. Structural proteins are encoded after the polymerase/replicase genes by mRNAs 2 (Spike protein), 3, 4 (Envelope protein), 5 (Membrane protein), and 9. mRNA 3 and 9 are bicistronic, the proteins 3a and 9a (Nucleocapsid protein) having functions in virus assembly and structure. Translation happens in the ER with the exception of 9a which is translated by cytosolic free ribosomes (Fung and Liu, 2019).

Literature references

Fung, TS., Liu, DX. (2019). Human Coronavirus: Host-Pathogen Interaction. *Annu. Rev. Microbiol., 73*, 529-557. ↗

Editions

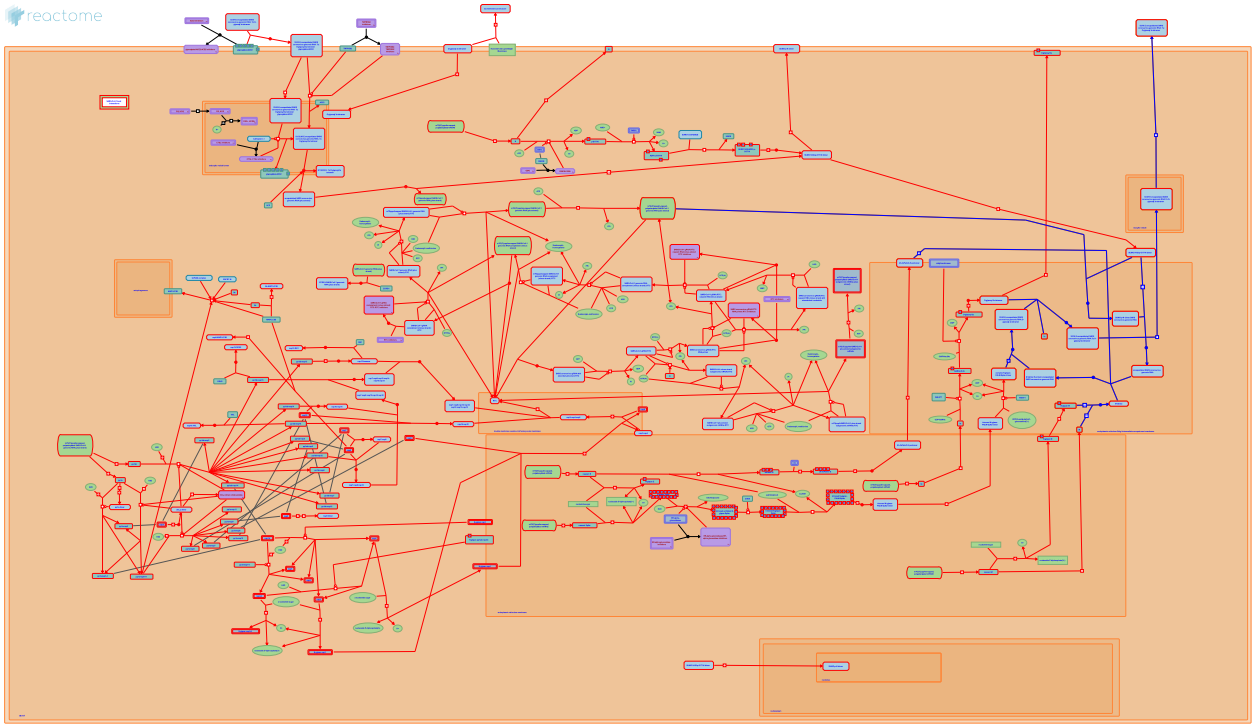
2020-04-08	Authored	Stephan, R.
2020-05-21	Edited	D'Eustachio, P.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

Virion Assembly and Release ↗

Location: SARS-CoV-1 Infection

Stable identifier: R-HSA-9679509

Diseases: severe acute respiratory syndrome



SARS viral assembly occurs at the ERGIC membrane (reviewed in Masters, 2006; Fehr and Perlman, 2015; Fung and Liu, 2019). Membrane protein components of the virus concentrate at the ERGIC membrane but are also found throughout the secretory system including at the plasma membrane. Accumulation at the site of viral assembly has been shown to depend on interaction between retrieval signals in the cytoplasmic tails of viral proteins and host factors such as the COPI coat, and likely involves repeated rounds of anterograde and retrograde traffic (McBride et al, 2007; Ujike et al, 2016; Tan et al, 2004; Tan et al, 2005; reviewed in McBride and Fielding, 2012; Chang et al, 2014).
Viral assembly is intitiated by homotypic interactions of M protein (Tseng et al, 2010; Siu et al, 2008). This forms an M-lattice that contributes to the induction of membrane curvature and additionally acts as a scaffold for the recruitment of the other structural components of the virus (Voss et al, 2009). M protein makes interactions with each of the main components of the mature virus, including E, S and N (He et al, 2004; Luo et al, 2006; Siu et al, 2008; reviewed in Masters, 2006). Electron micrographic studies suggest the final size of the mature virus is ~100 nm. The ribonuclear particle is predominantly helical and is packaged with an outer diamter of ~ 16 nm (Neuman et al, 2006; Neuman et al, 2011; reviewed in Chang et al, 2014). These physical constraints suggest a final stoichiometry in the mature virion of 75 S trimers:1200 M proteins:300 N:1 RNA genome (Neuman et al, 2011; reviewed in Chang et al, 2014). Minor amounts of other viral proteins, including proteins E, 3a and 7a may also be components of the mature virus, although their functions are not well established (reviewed in Schoeman and Fielding, 2019; Liu et al, 2014).

Literature references

Tseng, YT., Wang, SM., Chiang, CC., Huang, KJ., Lee, AI., Wang, CT. (2010). Self-assembly of severe acute respiratory syndrome coronavirus membrane protein. *J. Biol. Chem., 285*, 12862-72. ↗

Schoeman, D., Fielding, BC. (2019). Coronavirus envelope protein: current knowledge. *Virol. J., 16*, 69. ↗

Neuman, BW., Buchmeier, MJ., Milligan, RA., Yeager, M., Adair, BD., Orca, G. et al. (2006). Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. *J. Virol., 80*, 7918-28 . ↗

Li, Y., Tyler, S., Strocher, U., Booth, TF., Theriault, S., Bastien, N. et al. (2004). Characterization of protein-protein interactions between the nucleocapsid protein and membrane protein of the SARS coronavirus. *Virus Res., 105*, 121-5. ↗

Perlman, S., Fehr, AR. (2015). Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol. Biol., 1282*, 1-23. ↗

Editions

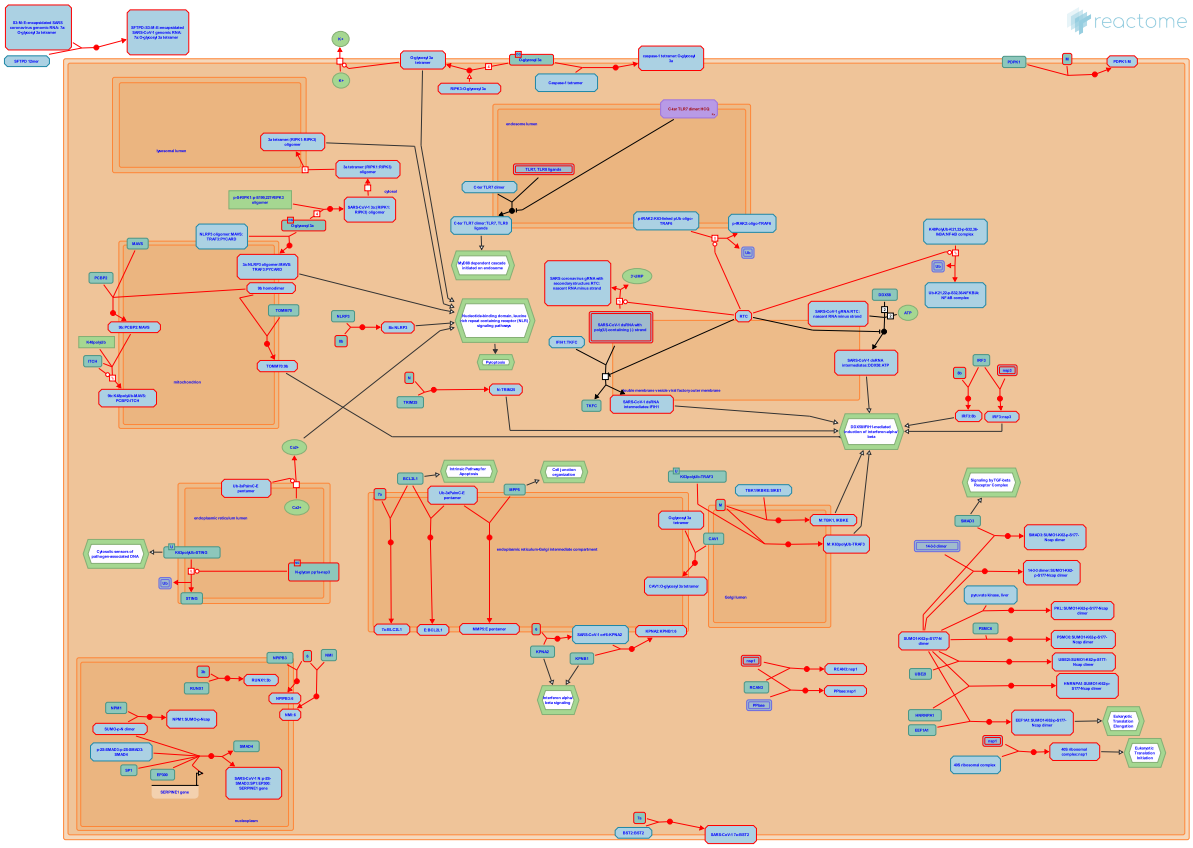
2020-04-22	Authored	Rothfels, K.
2020-04-23	Edited	Rothfels, K.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

SARS-CoV-1-host interactions ↗

Location: SARS-CoV-1 Infection

Stable identifier: R-HSA-9692914

Diseases: severe acute respiratory syndrome



Coronaviruses are a group of enveloped viruses with single-stranded, positive-sense RNA genomes. Each of the steps of viral replication - attachment and entry, translation of viral replicase, genome transcription and replication, translation of structural proteins, and virion assembly and release - involves host factors. These interactions can cause alterations in cellular structure and physiology, and activate host stress responses, autophagy, cell death, and processes of innate immunity (Fung TS & Liu DX 2019). This Reactome module describes molecular mechanisms by which severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) modulates host cell death pathways, innate immune responses, translation, intracellular signaling and regulatory pathways, and PDZ-mediated cell-cell junctions.

Literature references

Dunham, I., Kehrer, T., Southworth, DR., Alessi, DR., García-Sastre, A., Jura, N. et al. (2020). Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms. *Science, 370*. ↗

Fung, TS., Liu, DX. (2019). Human Coronavirus: Host-Pathogen Interaction. *Annu. Rev. Microbiol., 73*, 529-557. ↗

Editions

2020-06-25	Authored	Shamovsky, V.
2021-01-26	Reviewed	D'Eustachio, P.
2021-05-12	Authored	Stephan, R.
2022-08-11	Edited	Shamovsky, V.

Table of Contents