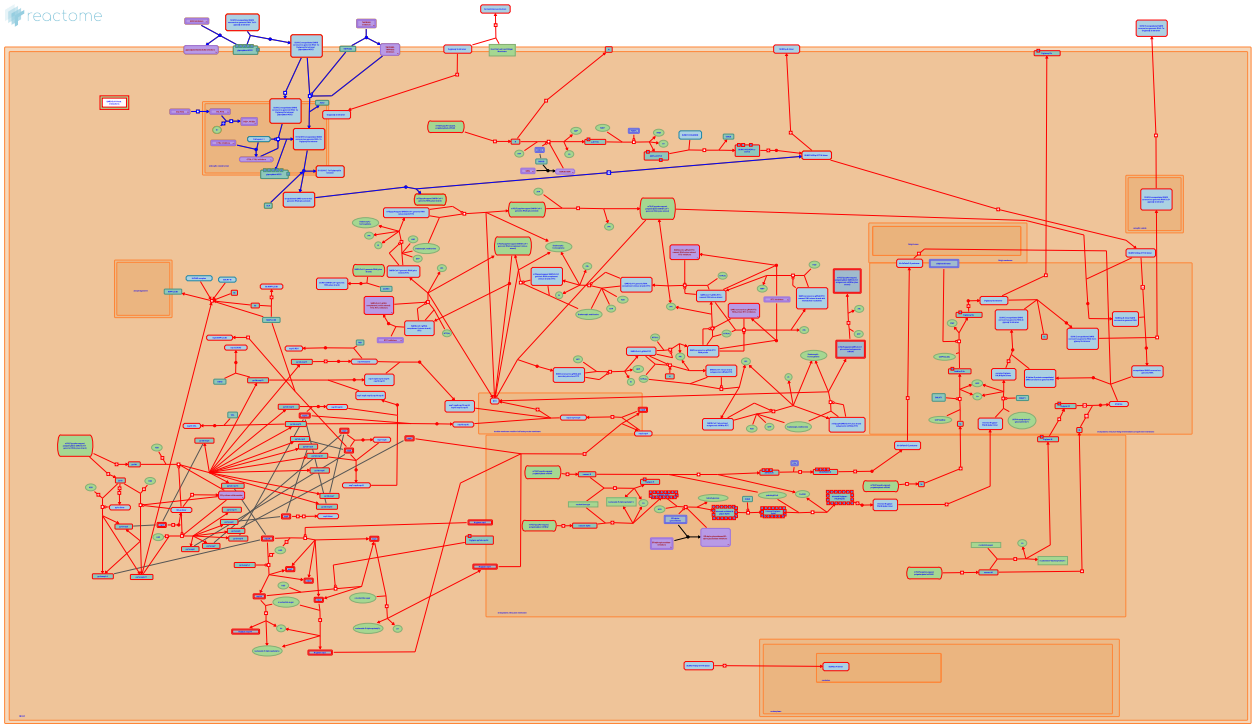
Attachment and Entry



Acencio, ML., D'Eustachio, P., Gillespie, ME., Jassal, B., Mazein, A., Stephan, R.

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

06/05/2024

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).

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. ↗

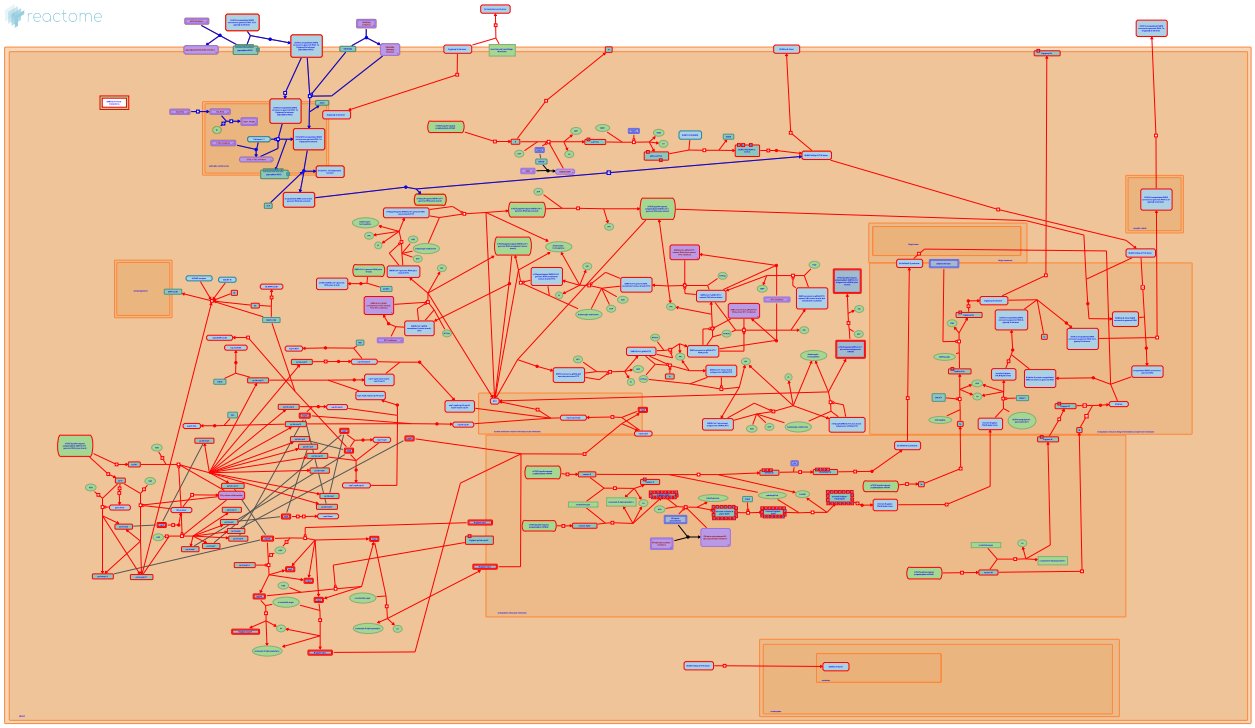
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Attachment and Entry ↗

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.

Spike glycoprotein of SARS coronavirus binds ACE2 on host cell

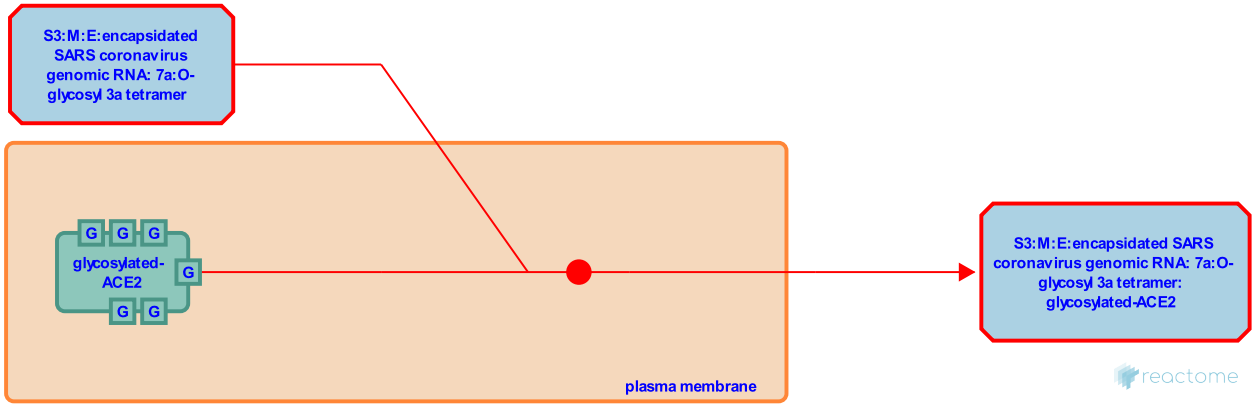
Location: Attachment and Entry

Stable identifier: R-HSA-9678128

Type: binding

Compartments: plasma membrane

Diseases: severe acute respiratory syndrome



SARS-CoV-1 spike (S3a) protein, as a component of the S3:M:E:encapsidated SARS coronavirus genomic RNA: 7a:O-glycosyl 3a tetramer complex, binds to glycosylated angiotensin converting enzyme 2 (ACE2) associated with the human host cell plasma membrane. Structural studies of the interaction between human ACE2 protein and the receptor-binding domain of S3a protein have identified key amino acid residues in both proteins responsible for their high-affinity interaction. These residues may be a key factor determining severity (and possibly human-to-human transmission) of SARS-CoV-1 (Li et al. 2003, 2005). The roles of S protein in viral binding to the host cell membrane and fusion of viral and host cell membranes and thus the central role of S protein in determining the host range and tissue tropisms of the virus are reviewed by Belouzard et al. (2012).

Followed by: TMPRSS2 Mediated SARS-CoV-1 Spike Protein Cleavage and Endocytosis, Endocytois of SARS-CoV-1 Virion

Literature references

Sui, J., Vasilieva, N., Farzan, M., Berne, MA., Luzuriaga, K., Somasundaran, M. et al. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature, 426*, 450-4.

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Licitra, BN., Belouzard, S., Millet, JK., Whittaker, GR. (2012). Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses, 4*, 1011-33.

Li, Y., Penninger, JM., Zhang, H., Slutsky, AS., Zhong, N. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med, 46*, 586-590.

Editions

2020-04-22	Authored	Gillespie, ME.
2020-05-21	Edited	D'Eustachio, P.
2020-05-26	Edited	Gillespie, ME.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

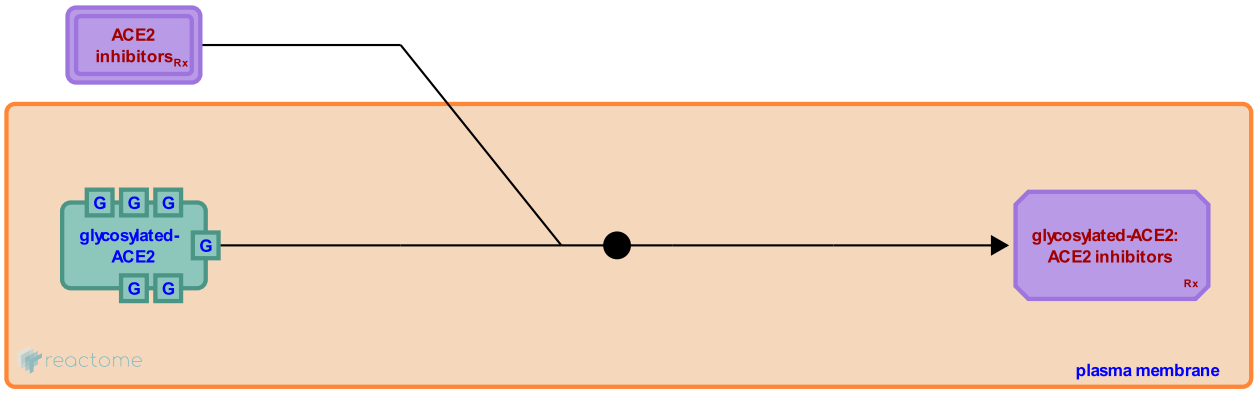
glycosylated-ACE2 binds ACE2 inhibitors ↗

Location: Attachment and Entry

Stable identifier: R-HSA-9695415

Type: binding

Compartments: plasma membrane, extracellular region



The CORDITE database contains aggregated information from published and preprint articles about potential drugs, their targets and their interactions (Martin et al. 2020). Different computational approaches reveal drug candidates that may be repurposed for the Covid-19 pandemic. The data provide by this database should be treated as interesting starting points for approved drug candidates that would require clinical testing to determine their efficacy specifically in Covid-19 patients. Here, potential drug candidates for the human ACE2 receptor are described.

Fan et al. constructed a pangolin coronavirus model to screen 2406 approved drugs for their ability to inhibit cytopathic effects and thereby identify candidates for treating Covid-19 infection (Fan et al. 2020). Three drugs, cepharanthine, selamectin and mefloquine hydrochloride, exhibited complete inhibition of cytopathic effects in cell culture. Selamectin is excluded from inclusion here as it is a vetinary drug not approved for human use.

Using Human Pluripotent Stem Cell-derived Colonic Organoids (hPSC-COs) and humanized mouse models, Duan et al. 2020 screened 1280 FDA-approved drugs, which uncovered mycophenolic acid and quinacrine dihydrochloride as promising candidates for SARS-CoV-2 entry inhibition, with greater efficacy than drugs currently being investigated for therapeutic use in COVID-19 (preprint https://www.biorxiv.org/content/10.1101/2020.05.02.073320v1.full).

Molecular dynamic simulations of SARS-CoV-2 spike protein and human ACE2 receptor complexes with stilbenoid analogues potentially having activities against these targets revealed resveratrol to have good affinity for the spike:ACE2 complex. Resveratrol could be a promising anti-COVID-19 drug candidate acting through disruption of the spike protein (Wahedi et al. 2020).

Using a virtual screen of the main targets involved in Covid-19 infection with 7922 FDA-approved drugs, Durdagi et al. 2020 ranked compounds based on their docking scores. Promising ACE2 receptor-binding domain inhibitors included denopamine and rotigaptide amongst the top 5 hits. These compounds could be clinically tested to check whether they may be considered to be use for the treatment of COVID-19 patients (preprint https://chemrxiv.org/articles/preprint/Screening_of_Clinically_Approved_and_Investigation_Drugs_as_Potential_Inhibitors_of_COVID-19_Main_Protease_A_Virtual_Drug_Repurposing_Study/12032712).

Using an in-silico structure-based virtual screening approach, Choudhary et al. 2020 found the FDA-approved drug eptifibatide acetate bound to the virus binding motifs of the ACE2 receptor (preprint https://chemrxiv.org/articles/preprint/Identification_of_SARS-CoV-2_Cell_Entry_Inhibitors_by_Drug_Repurposing_Using_in_Silico_Structure-Based_Virtual_Screening_Approach/12005988).

Redka et al. 2020 utilised a deep learning drug design platform to interrogate the polypharmacological profiles of FDA-approved small molecule drugs or going through clinical trials, with the goal of identifying molecules predicted to modulate targets relevant for COVID-19 treatment. Top drug hits predicted to bind to the ACE2 receptor included a number of broad-spectrum antibiotics such as latamoxef, cefazolin, cefoxitin, enoxacin and pheneticillin, amongst others. This study may identify and prioritise candidates for testing in Covid-19 patients (preprint https://chemrxiv.org/articles/preprint/PolypharmDB_a_Deep_Learning-

Based_Resource_Quickly_Identifies_Repurposed_Drug_Candidates_for_COVID-19/12071271)

In a study mining electronic health records, usage of diphenhydramine, hydroxyzine and azelastine was associated with reduced incidence of SARS-CoV-2 positivity in subjects greater than age 61 (Reznikov et al, 2020). Generally lower COVID19 incidence in people taking antihistamines was seen in a large observational study (Vila-Córcoles et al, 2020). Subsequently it was found that several H1 receptor antagonists are potent ACE2 inhibitors and potential COVID19 therapeutics: hydroxyzine (Reznikov et al, 2020) azelastine (Reznikov et al, 2020; Ge et al, 2021a), doxepin (Ge et al, 2021b), loratadine and desloratadine (Hou et al, 2021).
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Literature references

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Hou, Y., He, H., Wang, C., He, L., Ge, S., Li, X. (2021). Testing of the inhibitory effects of loratadine and desloratadine on SARS-CoV-2 spike pseudotyped virus viropexis. *Chem Biol Interact, 338*, 109420. ↗

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Ahmad, S., Wahedi, HM., Abbasi, SW. (2020). Stilbene-based natural compounds as promising drug candidates against COVID-19. *J. Biomol. Struct. Dyn.*, 1-10. ↗

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Editions

2020-07-13	Authored, Edited	Jassal, B.
2020-09-09	Reviewed	Acencio, ML.
2021-06-08	Revised	Stephan, R.

Endocytois of SARS-CoV-1 Virion ↗

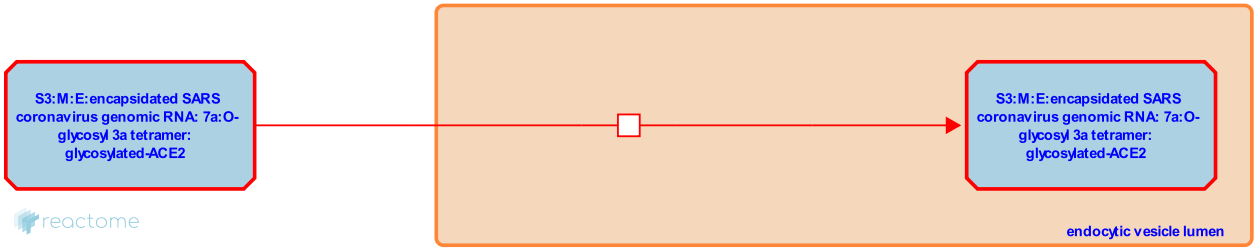
Location: Attachment and Entry

Stable identifier: R-HSA-9686711

Type: transition

Compartments: endocytic vesicle lumen

Diseases: severe acute respiratory syndrome



SARS-CoV-1 virions attached to the host cell surface via a complex involving viral spike (S) protein and host angiotensin-converting enzyme 2 (ACE2) undergo endocytosis. Studies with pseudoviruses have established that S protein is necessary and sufficient for mediating viral attachment and entry. Inhibition of this SARS-CoV-1 S protein-mediated transduction by two different classes of lysosomotropic agents in multiple cell lines strongly suggests that acidification of endosomes is needed for viral entry (Hofmann et al. 2004; Simmons et al. 2004; Yang et al. 2004). The roles of S protein in viral binding to the host cell membrane and fusion of viral and host cell membranes and thus the central role of S protein in determining the host range and tissue tropisms of the virus are reviewed by Belouzard et al. (2012).

Preceded by: Spike glycoprotein of SARS coronavirus binds ACE2 on host cell

Followed by: Cleavage of S protein into S1:S2

Literature references

Niedrig, M., Krumbiegel, M., Pöhlmann, S., Gramberg, T., Kuate, S., Marzi, A. et al. (2004). S protein of severe acute respiratory syndrome-associated coronavirus mediates entry into hepatoma cell lines and is targeted by neutralizing antibodies in infected patients. *J. Virol., 78*, 6134-42. ↗

Leung, K., Kong, WP., Huang, Y., Subbarao, K., Nabel, GJ., Yang, ZY. et al. (2004). pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN. *J. Virol., 78*, 5642-50. ↗

Licitra, BN., Belouzard, S., Millet, JK., Whittaker, GR. (2012). Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses, 4*, 1011-33. ↗

Bates, P., Piefer, AJ., Reeves, JD., Simmons, G., Amberg, SM., Rennekamp, AJ. (2004). Characterization of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. *Proc. Natl. Acad. Sci. U.S.A., 101*, 4240-5. ↗

Editions

2020-05-26	Authored, Edited	Gillespie, ME.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

Cleavage of S protein into S1:S2 ↗

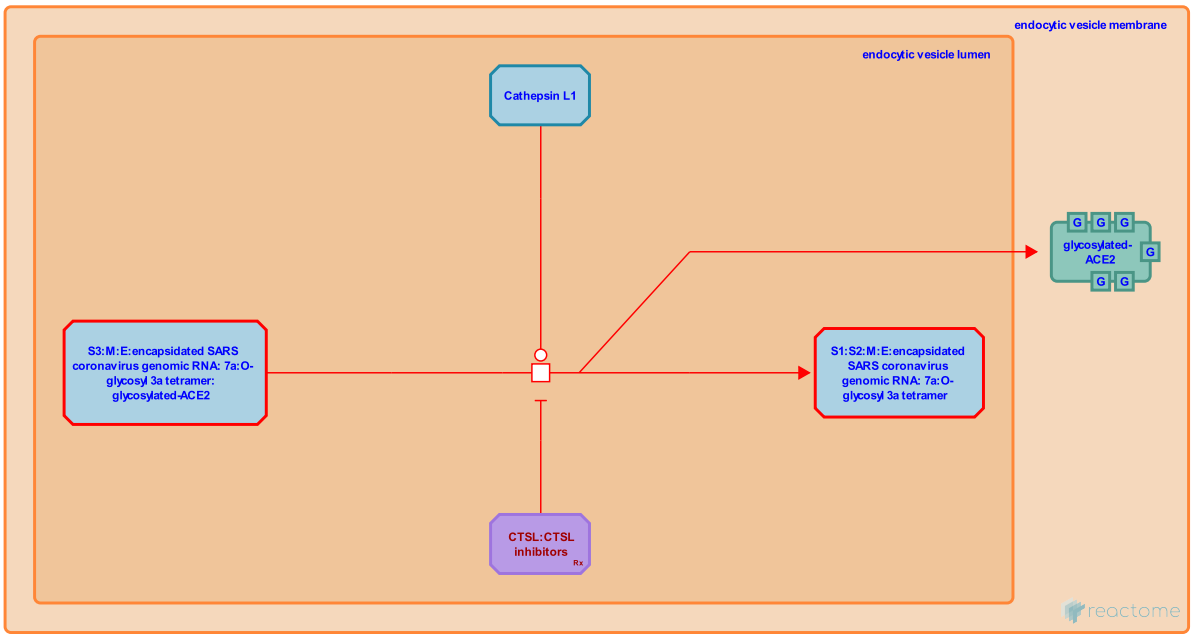
Location: Attachment and Entry

Stable identifier: R-HSA-9686710

Type: transition

Compartments: endocytic vesicle lumen

Diseases: severe acute respiratory syndrome



Spike protein S1: attaches the virion to the cell membrane by interacting with host receptor, initiating the infection.

Spike protein S2: Acts as a viral fusion peptide which is unmasked following S2 cleavage occurring upon virus endocytosis.

Spike protein S2: mediates fusion of the virion and cellular membranes by acting as a class I viral fusion protein. Under the current model, the protein has at least three conformational states: pre-fusion native state, pre-hairpin intermediate state, and post-fusion hairpin state. During viral and target cell membrane fusion, the coiled coil regions (heptad repeats) assume a trimer-of-hairpins structure, positioning the fusion peptide in close proximity to the C-terminal region of the ectodomain. The formation of this structure appears to drive apposition and subsequent fusion of viral and target cell membranes.

Within the host cell endocytic vesicle, SARS-CoV-1 Spike (S) protein is cleaved between residues 797 and 798 by cathepsin L1 (CTSL) (Huang et al. 2006). The roles of S protein in viral binding to the host cell membrane and fusion of viral and host cell membranes and thus the central role of S protein in determining the host range and tissue tropisms of the virus are reviewed by Belouzard et al. (2012).

Preceded by: Endocytois of SARS-CoV-1 Virion

Followed by: Fusion and Release of SARS-CoV-1 Nucleocapsid

Literature references

Licitra, BN., Belouzard, S., Millet, JK., Whittaker, GR. (2012). Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses, 4*, 1011-33. ↗

Belouzard, S., Chu, VC., Whittaker, GR. (2009). Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. *Proc. Natl. Acad. Sci. U.S.A., 106*, 5871-6. ↗

Editions

2020-05-05	Authored	Gillespie, ME.
2020-05-26	Edited	Gillespie, ME.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

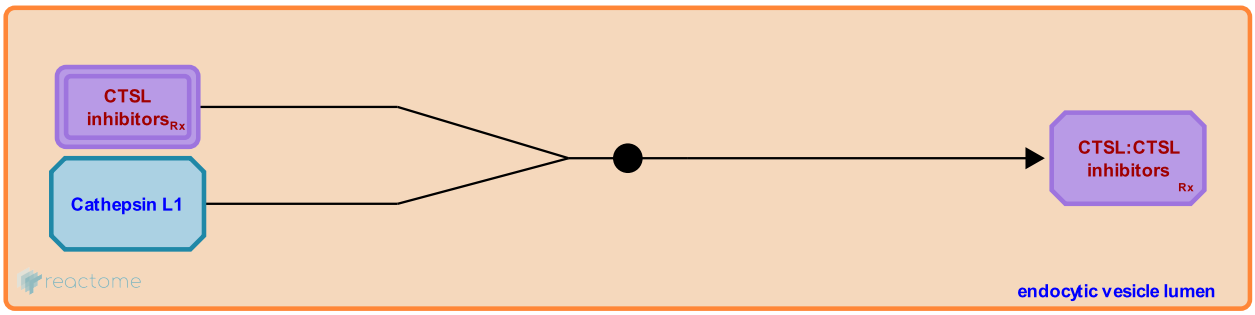
CTSL bind CTSL inhibitors ↗

Location: Attachment and Entry

Stable identifier: R-HSA-9685655

Type: binding

Compartments: endocytic vesicle lumen



Lysosomes play critical roles in human biology receiving, trafficking, processing, and degrading biological molecules from cellular processes such as endocytosis, phagocytosis, autophagy and secretion. Lysosomes house around sixty proteolytic enzymes, among them cathepsins. Cathepsins are involved in many processes involving cell death, protein degradation, post-translational modifications of proteins, extracellular matrix (ECM) remodeling, autophagy, and immune signaling. The early stages of the viral life cycle involve the cleavage of the viral spike protein by cathepsin L (CTSL) in late endosomes, facilitating viral RNA release to continue viral replication. Teicoplanin, a glycopeptide antibiotic used to treat Gram-positive bacterial infection, especially in Staphylococcal infections, was shown to have efficacy in vitro against Ebola Virus, MERS and SARS-CoV-1 (Zhou et al. 2016).

Teicoplanin is thought to inhibit the low pH cleavage of the viral spike protein by CTSL in late endosomes thereby preventing the release of genomic viral RNA and the continuation of virus replication cycle (Baron et al. 2020). The target sequence that serve as the cleavage site for CTSL is conserved in the SARS-CoV-2 spike protein (Zhou et al. 2020 [preprint]). Further investigation is required to determine the therapeutic potential of teicoplanin in COVID-19 patients.

Relacatib is an investigational drug trialed for the treatment of osteoporosis (Duong et al. 2016). It is a potent CTSK inhibitor but also shows activity against CTSL (Kumar et al. 2007) so could potentially be investigated for Covid-19 patients. The antileprotic drug clofazimine and the antituberculous drugs rifampicin and isoniazid have been shown to inhibit cathepsins B, H and L from purified goat and bovine brains (Kamboj et al. 2003).

Literature references

Zhang, L., Yang, FY., Yang, WL., Zhao, MM., Yang, JK., Feng, YM. et al. (2021). Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. *Signal Transduct Target Ther, 6*, 134. ↗

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Bai, C., Zhang, J., Peng, T., Zhou, N., Liu, C., Tao, L. et al. (2016). Glycopeptide Antibiotics Potently Inhibit Cathepsin L in the Late Endosome/Lysosome and Block the Entry of Ebola Virus, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). *J. Biol. Chem., 291*, 9218-32. ↗

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Oh, H., James, IE., Rickard, DJ., Stroup, G., Dare, L., Lark, MW. et al. (2007). A highly potent inhibitor of cathepsin K (relacatib) reduces biomarkers of bone resorption both in vitro and in an acute model of elevated bone turnover in vivo in monkeys. *Bone, 40*, 122-31. ↗

Editions

2020-04-24	Edited	Jassal, B.
2020-05-26	Edited	Gillespie, ME.
2020-09-09	Reviewed	Acencio, ML.
2020-09-09	Authored	Gillespie, ME.

Fusion and Release of SARS-CoV-1 Nucleocapsid ↗

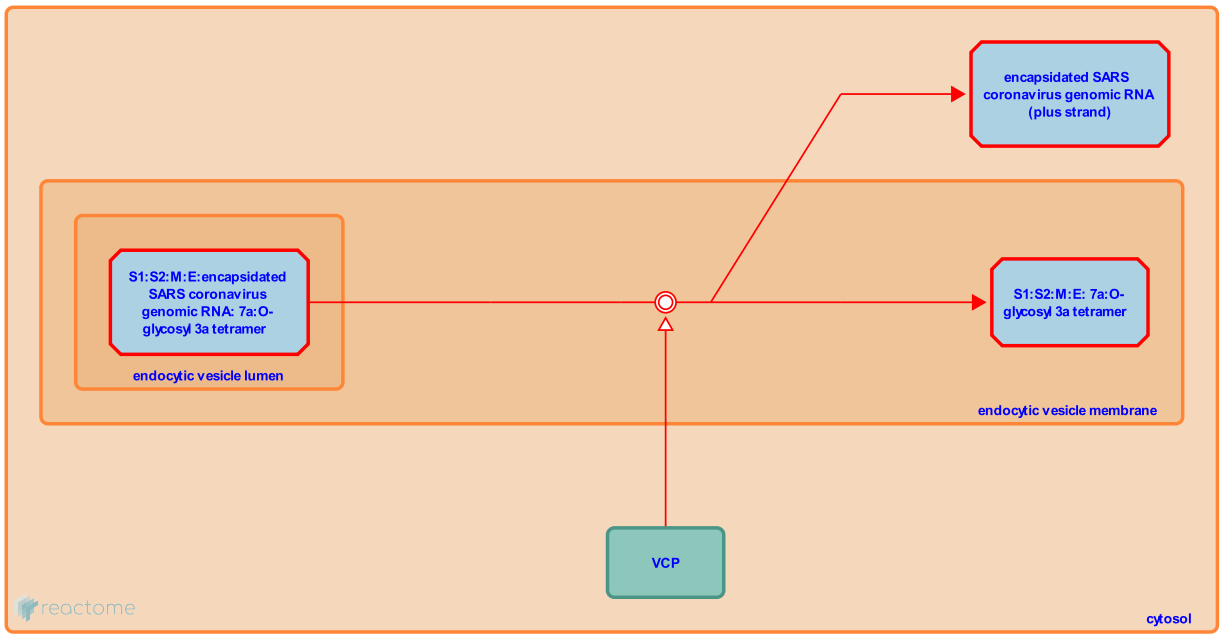
Location: Attachment and Entry

Stable identifier: R-HSA-9686699

Type: dissociation

Compartments: endocytic vesicle membrane

Diseases: severe acute respiratory syndrome



The SARS-CoV-1 nucleocapsid is released from the host cell endosome into the cytosol. Molecular details of this step are not well worked out. Studies of the infection of the human cultured cells with HCoV-229E coronavirus established a requirement for VCP (transitional endoplasmic reticulum ATPase) protein function for release to occur (Wong et al. 2015). A similar requirement for VCP involvement in SARS-CoV-1 nucleocapsid release is inferred here.

Preceded by: TMPRSS2 Mediated SARS-CoV-1 Spike Protein Cleavage and Endocytosis, Cleavage of S protein into S1:S2

Followed by: Uncoating of SARS-CoV-1 Genome

Literature references

Liu, DX., Moreau, D., Wong, HH., Tay, FP., Bard, F., Kumar, P. (2015). Genome-Wide Screen Reveals Valosin-Containing Protein Requirement for Coronavirus Exit from Endosomes. *J. Virol., 89*, 11116-28. ↗

Editions

2020-05-05	Authored	Gillespie, ME.
2020-05-26	Edited	Gillespie, ME.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

TMPRSS2 Mediated SARS-CoV-1 Spike Protein Cleavage and Endocytosis ↗

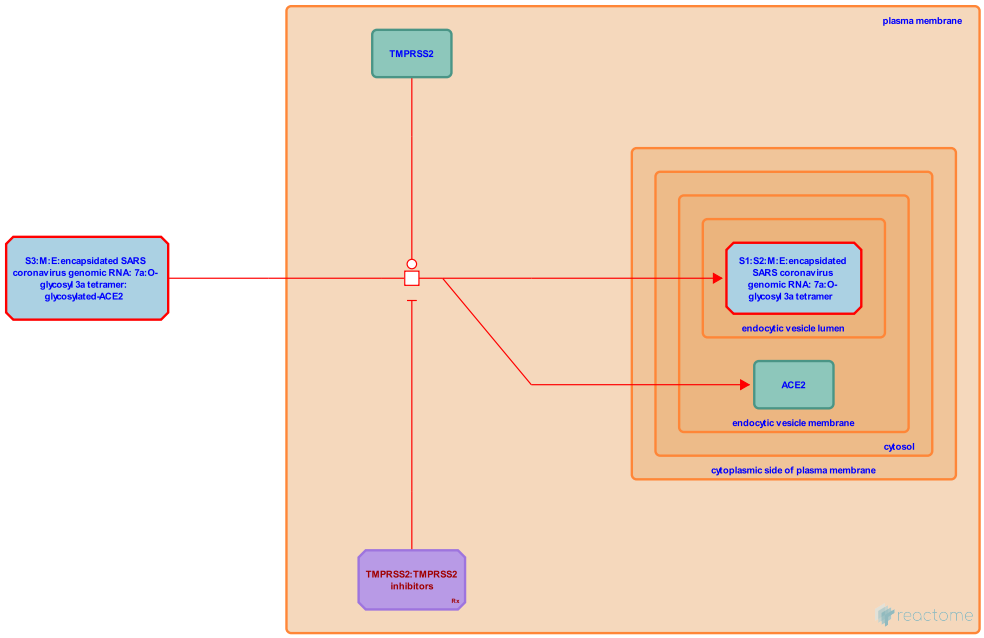
Location: Attachment and Entry

Stable identifier: R-HSA-9686731

Type: transition

Compartments: plasma membrane

Diseases: severe acute respiratory syndrome



Transmembrane protease serine 2 (TMPRSS2), associated with the plasma membrane of the host cell, mediates the hydrolytic cleavage of SARS-CoV-1 Spike (S) protein component of the viral membrane-associate S3:M:E:encapsidated SARS coronavirus genomic RNA: 7a:O-glycosyl 3a tetramer complex associated with ACE2 (Matsuyama et al. 2010; Glowacka et al. 2011; Shulla et al. 2011).

Preceded by: Spike glycoprotein of SARS coronavirus binds ACE2 on host cell

Followed by: Fusion and Release of SARS-CoV-1 Nucleocapsid

Literature references

Kawase, M., Nagata, N., Shirato, K., Matsuyama, S., Takeda, M., Taguchi, F. (2010). Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. *J. Virol., 84*, 12658-64. ↗

Perlman, S., Shulla, A., Zhao, J., Gallagher, T., Heald-Sargent, T., Subramanya, G. (2011). A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. *J. Virol., 85*, 873-82. ↗

Glowacka, I., Drosten, C., Niemeyer, D., He, Y., Bertram, S., Steffen, I. et al. (2011). Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *J. Virol., 85*, 4122-34. ↗

Editions

2020-05-05	Authored	Gillespie, ME.
2020-05-26	Edited	Gillespie, ME.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

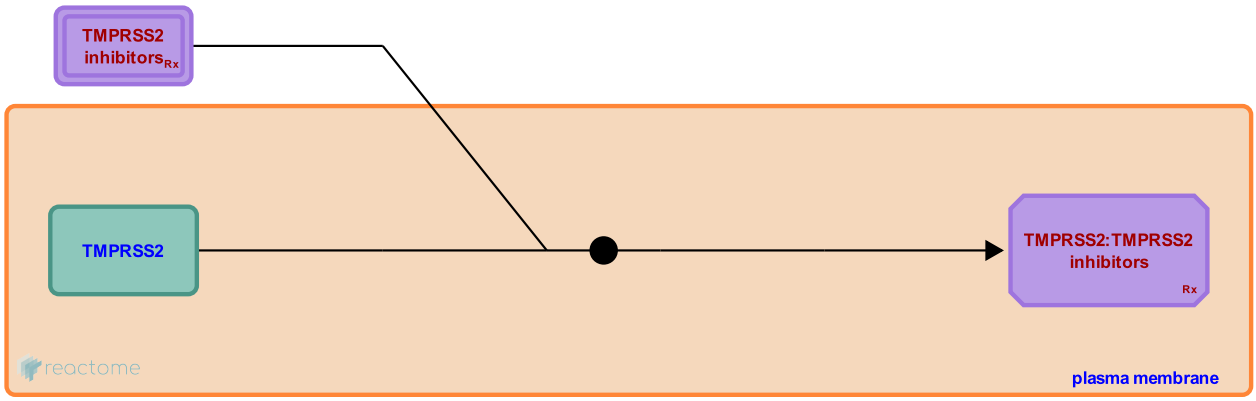
TMPRSS2 binds TMPRSS2 inhibitors ↗

Location: Attachment and Entry

Stable identifier: R-HSA-9681514

Type: binding

Compartments: plasma membrane, extracellular region



Entry of influenza, parainfluenza and coronaviruses into airway epithelial cells requires binding of a viral spike protein to a host cell receptor, followed by cleavage and activation of the viral spike protein mediated by the host cell. Without this cleavage, fusion of the viral and host cell membranes is blocked. The primary receptor for the human SARS-CoV-1 virus is angiotensin converting enzyme 2 (ACE2) (Li et al. 2003). The resultant complex is cleaved by the protease transmembrane protease serine 2 (TMPRSS2) (Shulla et al. 2011, Heurich et al. 2014). Therefore, active site inhibitors of these airway proteases could have broad therapeutic applicability against multiple respiratory viruses (Laporte & Naesens 2017). The approved drug camostat is a protease inhibitor that may block SARS-CoV-2 entry into cells by inhibiting the actions of TMPRSS2 (Kawase et al. 2012, Hoffmann et al. 2020). Nafamostat, another serine protease inhibitor, was found to be a potent inhibitor of S-mediated membrane fusion and blocked MERS-CoV infection in vitro (Yamamoto et al. 2016).

Otamixaban (FXV673), an anticoagulant, is a potent and selective direct inhibitor of coagulation factor Xa. Virtual docking studies suggest that otamixaban may bind to the serine protease TMPRSS2 (Rensi et al. 2020, preprint). Inhibition of TMPRSS2 is being examined for antiviral activity but its inhibitory potential and/or antiviral activity have not yet been determined so it is annotated here as a candidate drug. I-432 is another inhibitor of TMPRSS2 under investigation for anti viral potential (Pászti-Gere et al. 2016).

Literature references

Kawase, M., van der Hoek, L., Matsuyama, S., Shirato, K., Taguchi, F. (2012). Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. *J. Virol., 86*, 6537-45. ↗

Drosten, C., Herrler, G., Wu, NH., Krüger, N., Schroeder, S., Erichsen, S. et al. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* ↗

Jahn, O., Pöhlmann, S., Hofmann-Winkler, H., Heurich, A., Gierer, S., Liepold, T. (2014). TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. *J. Virol., 88*, 1293-307. ↗

Maiwald, A., Ujhelyi, G., Pászti-Gere, E., Balla, P., Czimmermann, E., Steinmetzer, T. (2016). In vitro characterization of TMPRSS2 inhibition in IPEC-J2 cells. *J Enzyme Inhib Med Chem, 31*, 123-129. ↗

Inoue, JI., Li, X., Matsuda, Z., Matsuyama, S., Takeda, M., Kawaguchi, Y. et al. (2016). Identification of Nafamostat as a Potent Inhibitor of Middle East Respiratory Syndrome Coronavirus S Protein-Mediated Membrane Fusion Using the Split-Protein-Based Cell-Cell Fusion Assay. *Antimicrob. Agents Chemother., 60*, 6532-6539. ↗

Editions

2020-04-02	Edited	Jassal, B.
2020-09-09	Reviewed	Acencio, ML.
2020-09-09	Authored	Gillespie, ME.

Uncoating of SARS-CoV-1 Genome ↗

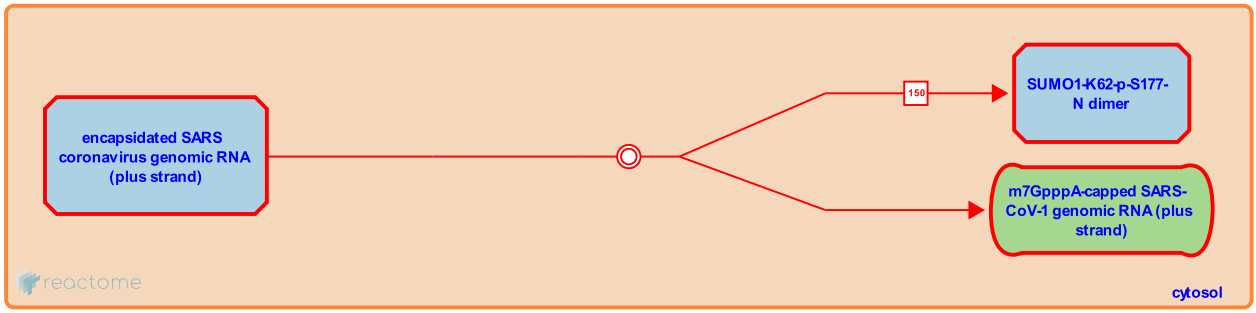
Location: Attachment and Entry

Stable identifier: R-HSA-9686709

Type: dissociation

Compartments: cytosol

Diseases: severe acute respiratory syndrome



The viral nucleocapsid complex, released into the host cell cytosol, dissociates to release the viral RNA genome (Fung & Liu 2019).

Preceded by: Fusion and Release of SARS-CoV-1 Nucleocapsid

Literature references

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

Editions

2020-05-05	Authored	Gillespie, ME.
2020-05-26	Edited	Gillespie, ME.
2020-05-27	Reviewed	Mazein, A., Acencio, ML.

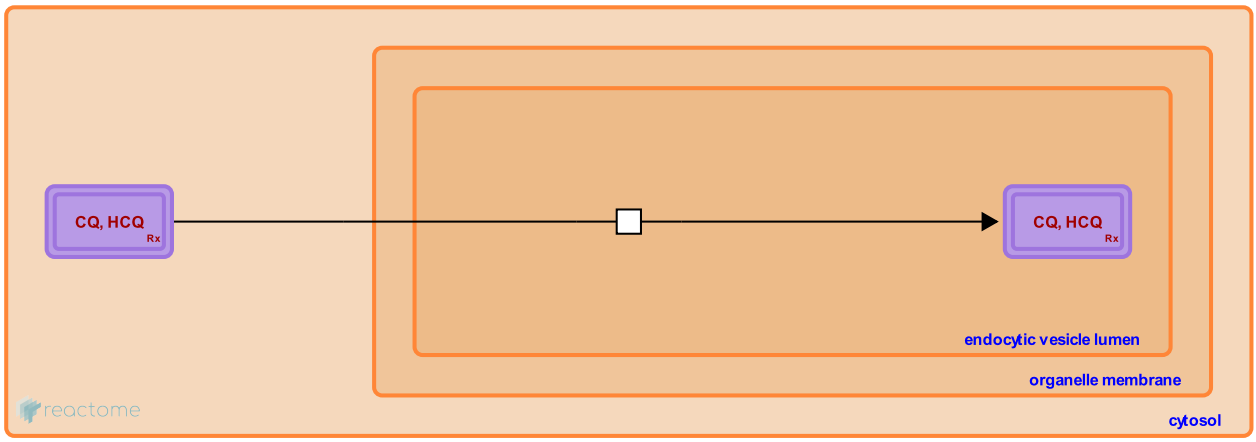
CQ, HCQ diffuses from cytosol to endocytic vesicle lumen ↗

Location: Attachment and Entry

Stable identifier: R-HSA-9683478

Type: transition

Compartments: endocytic vesicle lumen, cytosol



Unprotonated chloroquine (CQ) and hydroxychloroquine (HCQ) can both diffuse freely and rapidly across the membranes of cells and organelles (Chinappi et al. 2010).

Followed by: CQ, HCQ are protonated to CQ2+, HCQ2+

Literature references

Marcatili, P., Chinappi, M., Via, A., Tramontano, A. (2010). On the mechanism of chloroquine resistance in Plasmodium falciparum. *PLoS ONE, 5*, e14064. ↗

Editions

2020-04-16	Edited	Jassal, B.
2020-09-09	Reviewed	Acencio, ML.
2020-09-09	Authored	Gillespie, ME.

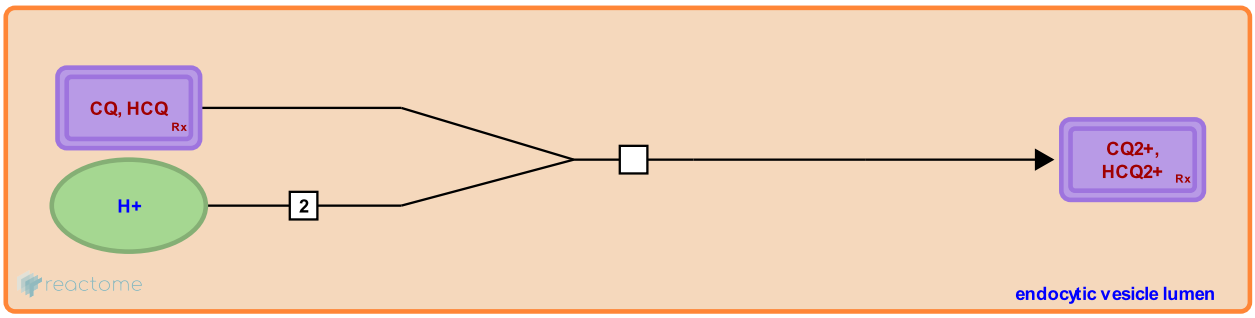
CQ, HCQ are protonated to CQ2+, HCQ2+ ↗

Location: Attachment and Entry

Stable identifier: R-HSA-9683467

Type: transition

Compartments: endocytic vesicle lumen



Chloroquine (CQ) and hydroxychloroquine (HCQ) are diprotic weak bases that can exist in both protonated and unprotonated forms. Unprotonated CQ or HCQ can diffuse freely and rapidly across the membranes of cells and organelles to acidic cytoplasmic vesicles (late endosomes and lysosomes). Agents that have this ability are known as lysosomotropic agents. Once protonated, CQ2+ or HCQ2+ are trapped in the acidic lumen of these vesicles. This leads to an irreversible accumulation of CQ or HCQ in acidic vesicles to concentrations as much as 100 fold over cytosolic ones and to an elevation of vesicle pH due to trapping of H+ ions by CQ or HCQ. Thus, CQ analogues interfere with endosomal and lysosomal acidification, which in turn inhibits proteolysis, chemotaxis, phagocytosis and antigen presentation. As a result, cells are not able to proceed with endocytosis, exosome release and phagolysosomal fusion in an orderly manner (Foley & Tilley 1998, Yang & Shen 2020). In vitro, these endosomal acidification fusion inhibitors block cellular infection by a clinical isolate of SARS-CoV-2 (Wang et al. 2020, Hu et al. 2020).

Preceded by: CQ, HCQ diffuses from cytosol to endocytic vesicle lumen

Literature references

Shen, HM., Yang, N. (2020). Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19. *Int. J. Biol. Sci., 16*, 1724-1731. ↗

Al-Bari, MAA. (2017). Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. *Pharmacol Res Perspect, 5*, e00293. ↗

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Tilley, L., Foley, M. (1998). Quinoline antimalarials: mechanisms of action and resistance and prospects for new agents. *Pharmacol. Ther., 79*, 55-87. ↗

Editions

2020-04-16	Edited	Jassal, B.
2020-09-09	Reviewed	Acencio, ML.
2020-09-09	Authored	Gillespie, ME.

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