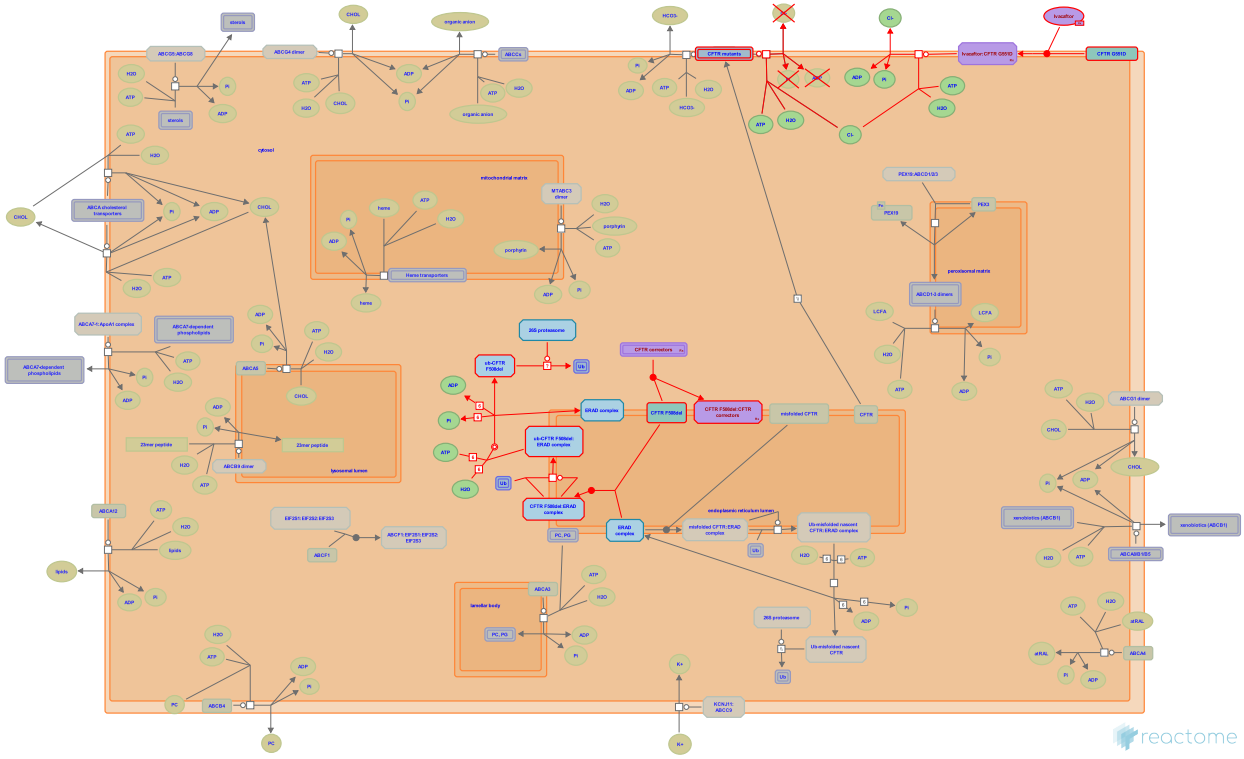
Defective CFTR causes cystic fibrosis



D'Eustachio, P., Huddart, R., Jassal, B., Matthews, L., Moitra, K., Rothfels, K.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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. ↗

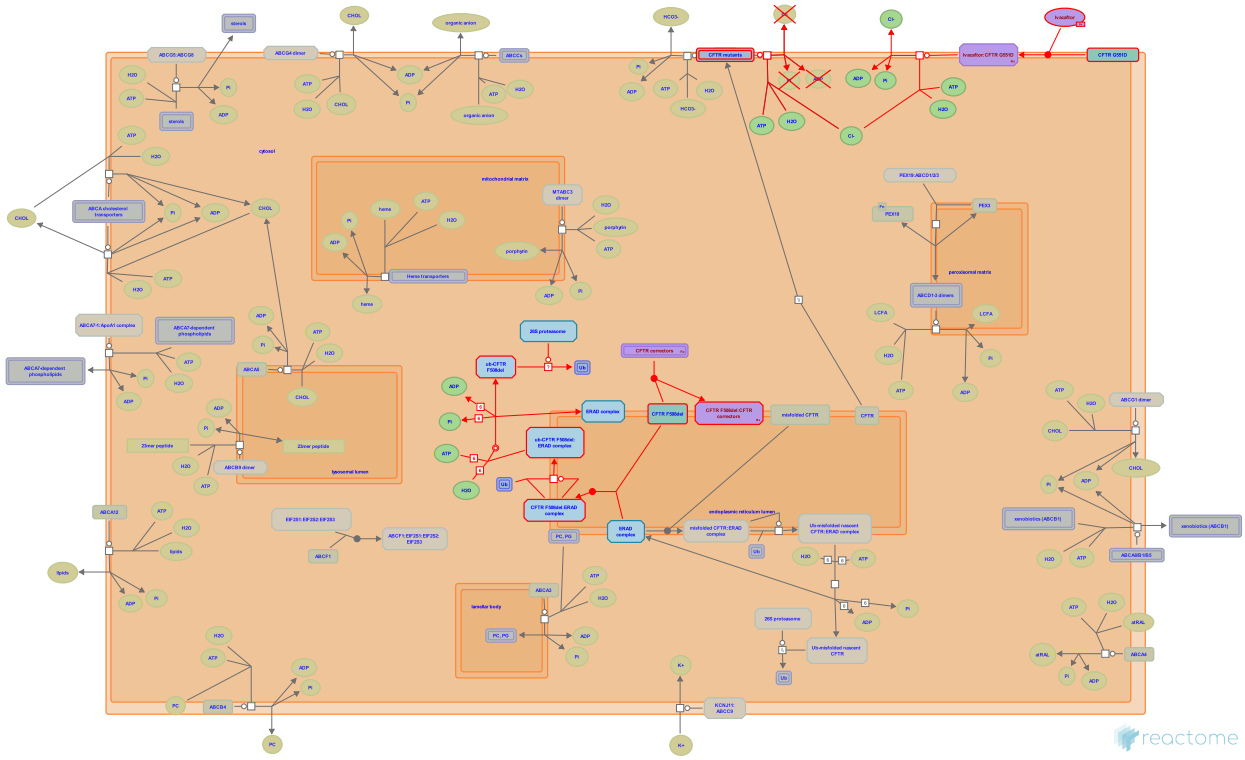
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Defective CFTR causes cystic fibrosis ↗

Stable identifier: R-HSA-5678895

Diseases: cystic fibrosis



Cystic fibrosis transmembrane conductance regulator (CFTR) is a low conductance chloride-selective channel that mediates the transport of chloride ions in human airway epithelial cells. Chloride ions plays a key role in maintaining homoeostasis of epithelial secretions in the lungs. Defects in CFTR can cause cystic fibrosis (CF; MIM:602421), a common generalised disorder in Caucasians affecting the exocrine glands. CF results in an ionic imbalance that impairs clearance of secretions, not only in the lung, but also in the pancreas, gastrointestinal tract and liver. Wide-ranging manifestations of the disease include chronic lung disease, exocrine pancreatic insufficiency, blockage of the terminal ileum, male infertility and salty sweat. The median survival of CF patients in North America and Western Europe is around 40 years (Davis 2006, Radlovic 2012).

Literature references

Rogan, MP., Stoltz, DA., Hornick, DB. (2011). Cystic fibrosis transmembrane conductance regulator intracellular processing, trafficking, and opportunities for mutation-specific treatment. *Chest, 139*, 1480-90. ↗

Markiewicz, D., Buchanan, JA., Buchwald, M., Kerem, B., Cox, TK., Tsui, LC. et al. (1989). Identification of the cystic fibrosis gene: genetic analysis. *Science, 245*, 1073-80. ↗

Davis, PB. (2006). Cystic fibrosis since 1938. *Am. J. Respir. Crit. Care Med., 173*, 475-82. ↗

Radlovi?, N. (2012). Cystic fibrosis. *Srp Arh Celok Lek, 140*, 244-9. ↗

Editions

2015-02-26	Authored, Edited	Jassal, B.
2015-04-28	Reviewed	Moitra, K.

Defective CFTR does not transport Cl- from cytosol to extracellular region ↗

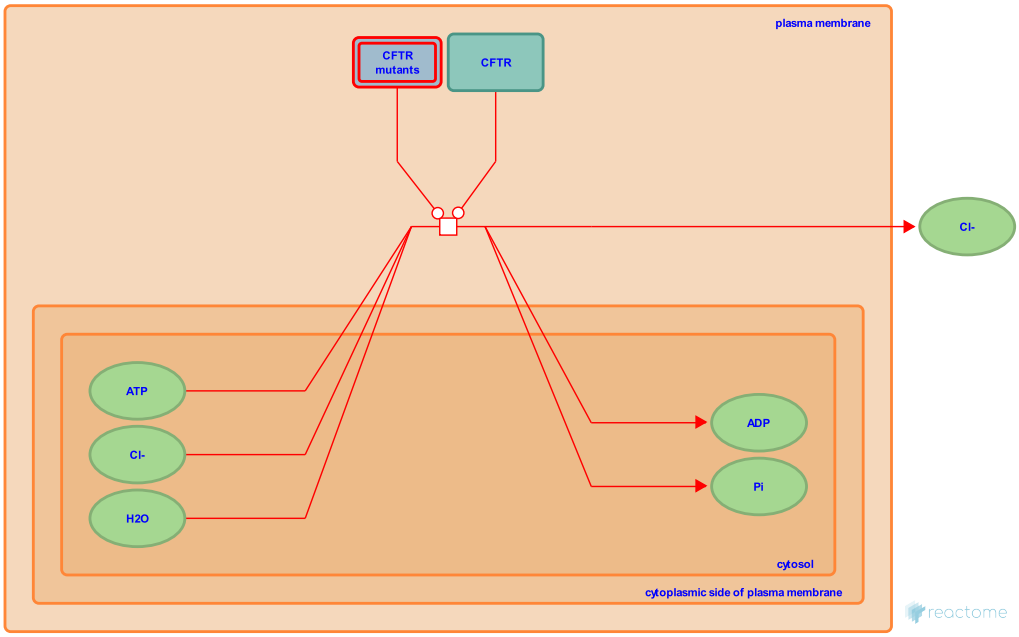
Location: Defective CFTR causes cystic fibrosis

Stable identifier: R-HSA-5678822

Type: transition

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cystic fibrosis



Cystic fibrosis transmembrane conductance regulator (CFTR) is a low conductance chloride-selective channel that mediates the transport of chloride ions in human airway epithelial cells. Chloride ions plays a key role in maintaining homoeostasis of epithelial secretions in the lungs. Defects in CFTR can cause cystic fibrosis (CF; MIM:602421), a common generalised disorder in Caucasians affecting the exocrine glands. CF results in an ionic imbalance that impairs clearance of secretions, not only in the lung, but also in the pancreas, gastrointestinal tract and liver. Wide-ranging manifestations of the disease include chronic lung disease, exocrine pancreatic insufficiency, blockage of the terminal ileum, male infertility and salty sweat.

The most common mutation that causes CF is F508del (Kerem et al. 1989). Although more than 1,500 mutations of CFTR have been identified, only four mutations besides F508del reach a frequency of 1% to 3%: G551D, W1282X, G542X, and N1303K (Rogan et al. 2011, Cutting et al. 1990, Vidaud et al. 1990, Kerem et al. 1990, Cuppens et al. 1990, Osborne et al. 1991).

Literature references

Rogan, MP., Stoltz, DA., Hornick, DB. (2011). Cystic fibrosis transmembrane conductance regulator intracellular processing, trafficking, and opportunities for mutation-specific treatment. *Chest, 139*, 1480-90. ↗

Van den Berghe, H., De Boeck, C., De Baets, F., Marynen, P., Cassiman, JJ., Cuppens, H. et al. (1990). A child, homozygous for a stop codon in exon 11, shows milder cystic fibrosis symptoms than her heterozygous nephew. *J. Med. Genet., 27*, 717-9. ↗

Antonarakis, SE., Kazazian, HH., Cutting, GR., Kasch, LM., Tsui, LC., Rosenstein, BJ. et al. (1990). A cluster of cystic fibrosis mutations in the first nucleotide-binding fold of the cystic fibrosis conductance regulator protein. *Nature , 346*, 366-9. ↗

Markiewicz, D., Collins, FS., Kennedy, D., Gazit, E., Bozon, D., Riordan, JR. et al. (1990). Identification of mutations in regions corresponding to the two putative nucleotide (ATP)-binding folds of the cystic fibrosis gene. *Proc. Natl. Acad. Sci. U.S.A., 87*, 8447-51. ↗

Martin, J., Nicolas, S., Goossens, M., Ghanem, N., Fanen, P., Vidaud, M. (1990). Three point mutations in the CFTR gene in French cystic fibrosis patients: identification by denaturing gradient gel electrophoresis. *Hum. Genet., 85*, 446-9. ↗

Editions

2015-02-26	Authored, Edited	Jassal, B.
2015-04-28	Reviewed	Moitra, K.

Ivacaftor binds CFTR G551D ↗

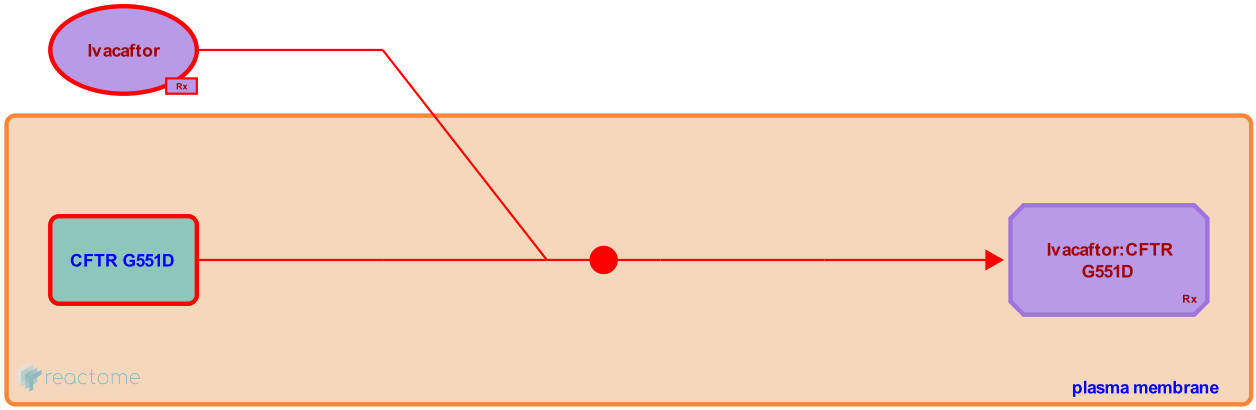
Location: Defective CFTR causes cystic fibrosis

Stable identifier: R-HSA-5679000

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: cystic fibrosis



Defects in cystic fibrosis transmembrane conductance regulator (CFTR) can cause cystic fibrosis (CF; MIM:602421), a common generalised disorder in Caucasians affecting the exocrine glands. CF results in an ionic imbalance that impairs clearance of secretions, not only in the lung, but also in the pancreas, gastrointestinal tract and liver. Wide-ranging manifestations of the disease include chronic lung disease, exocrine pancreatic insufficiency, blockage of the terminal ileum, male infertility and salty sweat. The class 3 mutations of CFTR such as G551D strongly decrease the time spent by CFTR in the open state (a gating defect). Results from 2-phase clinical trials using VX-770 (aka Ivacaftor), a CFTR potentiator, showed an increased CFTR channel open probability in G551D patients. Ivacaftor use showed improvements in CFTR and lung function of patients with at least one G551D allele (Accurso et al. 2010, Ramsey et al. 2011, Kapoor et al. 2014). In 2012, the FDA approved Ivacaftor (under the trade name Kalydeco) for use in cystic fibrosis patients with the G551D mutation (Ledford 2012).

Literature references

Rowe, SM., Ramsey, BW., Campbell, PW., Sagel, SD., Ashlock, MA., Clancy, JP. et al. (2010). Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N. Engl. J. Med., 363*, 1991-2003. ↗

Ledford, H. (2012). Drug bests cystic-fibrosis mutation. *Nature, 482*, 145. ↗

Singh, A., Kapoor, H., Koolwal, A. (2014). Ivacaftor: a novel mutation modulating drug. *J Clin Diagn Res, 8*, SE01-5. ↗

Moss, R., Davies, J., Rowe, SM., McKone, EF., Ratjen, F., Ramsey, BW. et al. (2011). A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N. Engl. J. Med., 365*, 1663-72. ↗

Editions

2015-02-27	Authored, Edited	Jassal, B.
2015-04-28	Reviewed	Moitra, K.

Ivacaftor:CFTR G551D transports Cl- from cytosol to extracellular region ↗

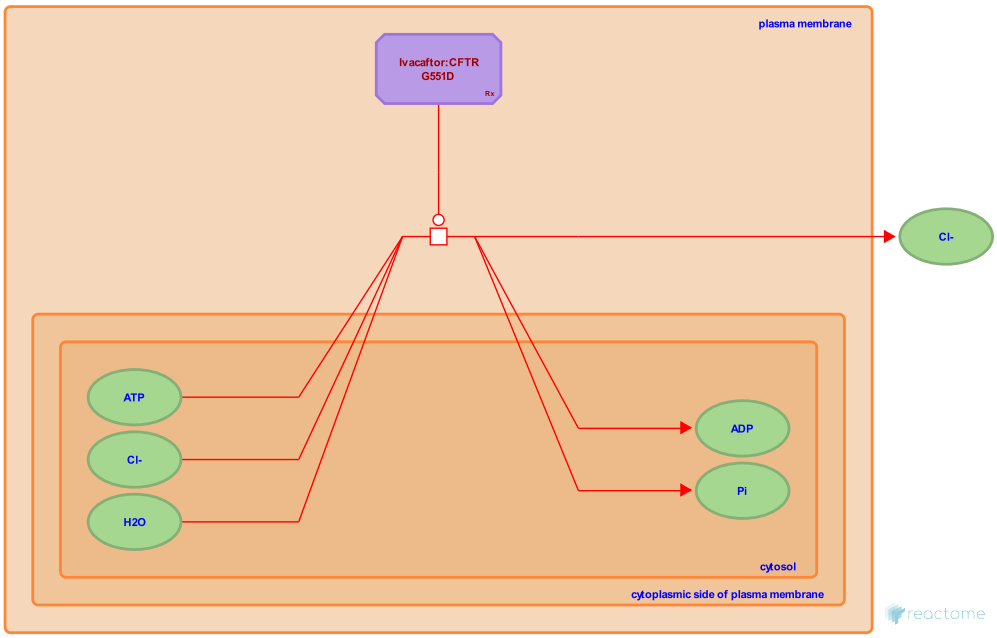
Location: Defective CFTR causes cystic fibrosis

Stable identifier: R-HSA-5678992

Type: transition

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cystic fibrosis



Cystic fibrosis transmembrane conductance regulator (CFTR) is a low conductance chloride-selective channel that mediates the transport of chloride ions in human airway epithelial cells which plays a key role in maintaining homoeostasis of epithelial secretions in the lungs. Defects in CFTR can cause cystic fibrosis (CF; MIM:602421), a common generalised disorder in Caucasians affecting the exocrine glands. CF results in an ionic imbalance that impairs clearance of secretions, not only in the lung, but also in the pancreas, gastrointestinal tract and liver. Wide-ranging manifestations of the disease include chronic lung disease, exocrine pancreatic insufficiency, blockage of the terminal ileum, male infertility and salty sweat.

The class 3 mutations of CFTR such as G551D strongly decrease the time spent by CFTR in the open state (a gating defect). Results from 2-phase clinical trials using VX-770 (aka Ivacaftor), a CFTR potentiator, showed an increased CFTR channel open probability in G551D patients. Ivacaftor use showed improvements in CFTR and lung function of patients with at least one G551D allele (Accurso et al. 2010, Ramsey et al. 2011, Kapoor et al. 2014). In 2012, the FDA approved Ivacaftor (under the trade name Kalydeco) for use in cystic fibrosis patients with the G551D mutation (Ledford 2012).

Literature references

Rowe, SM., Ramsey, BW., Campbell, PW., Sagel, SD., Ashlock, MA., Clancy, JP. et al. (2010). Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N. Engl. J. Med., 363*, 1991-2003. ↗

Ledford, H. (2012). Drug bests cystic-fibrosis mutation. *Nature, 482*, 145. ↗

Singh, A., Kapoor, H., Koolwal, A. (2014). Ivacaftor: a novel mutation modulating drug. *J Clin Diagn Res, 8*, SE01-5. ↗

Moss, R., Davies, J., Rowe, SM., McKone, EF., Ratjen, F., Ramsey, BW. et al. (2011). A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N. Engl. J. Med., 365*, 1663-72. ↗

Editions

2015-02-27	Authored, Edited	Jassal, B.
2015-04-28	Reviewed	Moitra, K.

CFTR F508del binds components of the ERAD machinery for ubiquitination and degradation ↗

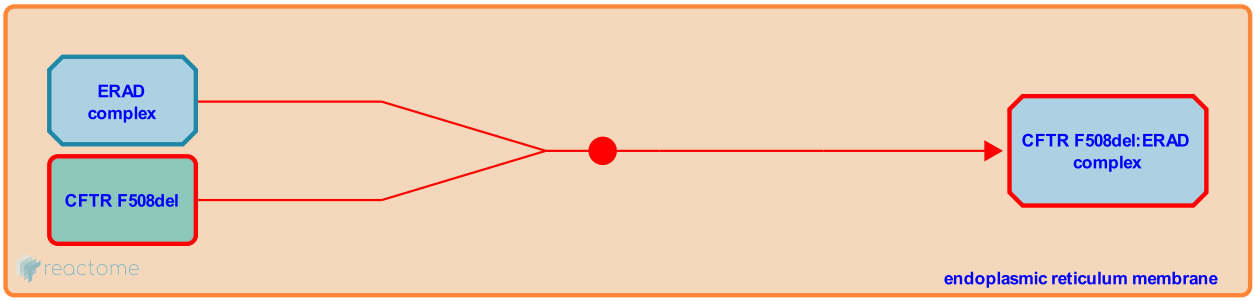
Location: Defective CFTR causes cystic fibrosis

Stable identifier: R-HSA-8866857

Type: binding

Compartments: endoplasmic reticulum membrane

Diseases: cystic fibrosis



Deletion of phenylalanine 508 in CFTR is the most prevalent mutation causing cystic fibrosis (Riordan et al, 1989; Kerem et al, 1989). F508 deletion causes destabilization and subsequent targeting for co-translational degradation by the ER-associated degradation machinery (ERAD). Like misfolded WT CFTR protein, F508del is ubiquitinated by ERAD-associated E3 ligases including RNF5 and RNF 185, targeting it for VCP-mediated retrotranslocation and 26S proteasomal degradation (Meachem et al, 2001; Rosser et al, 2008; Younger et al, 2004; Younger et al, 2006; El Khouri et al, 2013; reviewed in Pranke and Sermet-Gaudelus, 2014).

Followed by: RNF5 and RNF185 ubiquitinate CFTR F508del

Literature references

El Khouri, E., Toledano, MB., Le Pavec, G., Delaunay-Moisan, A. (2013). RNF185 is a novel E3 ligase of endoplasmic reticulum-associated degradation (ERAD) that targets cystic fibrosis transmembrane conductance regulator (CFTR). *J. Biol. Chem., 288*, 31177-91. ↗

Fields, A., Fan, CY., Ren, HY., Younger, JM., Cyr, DM., Chen, L. et al. (2004). A foldable CFTR{Delta}F508 biogenic intermediate accumulates upon inhibition of the Hsc70-CHIP E3 ubiquitin ligase. *J. Cell Biol., 167*, 1075-85. ↗

Fan, CY., Ren, HY., Rosser, MF., Younger, JM., Cyr, DM., Turnbull, EL. et al. (2006). Sequential quality-control checkpoints triage misfolded cystic fibrosis transmembrane conductance regulator. *Cell, 126*, 571-82. ↗

Grove, DE., Rosser, MF., Cyr, DM., Chen, L. (2008). Assembly and misassembly of cystic fibrosis transmembrane conductance regulator: folding defects caused by deletion of F508 occur before and after the calnexin-dependent association of membrane spanning domain (MSD) 1 and MSD2. *Mol. Biol. Cell, 19*, 4570-9. ↗

Chou, JL., Alon, N., Kerem, B., Riordan, JR., Rozmahel, R., Plavsic, N. et al. (1989). Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science, 245*, 1066-73. ↗

Editions

2016-04-02	Authored, Edited	Rothfels, K.
2016-04-23	Reviewed	D'Eustachio, P.

CFTR F508del binds CFTR correctors ↗

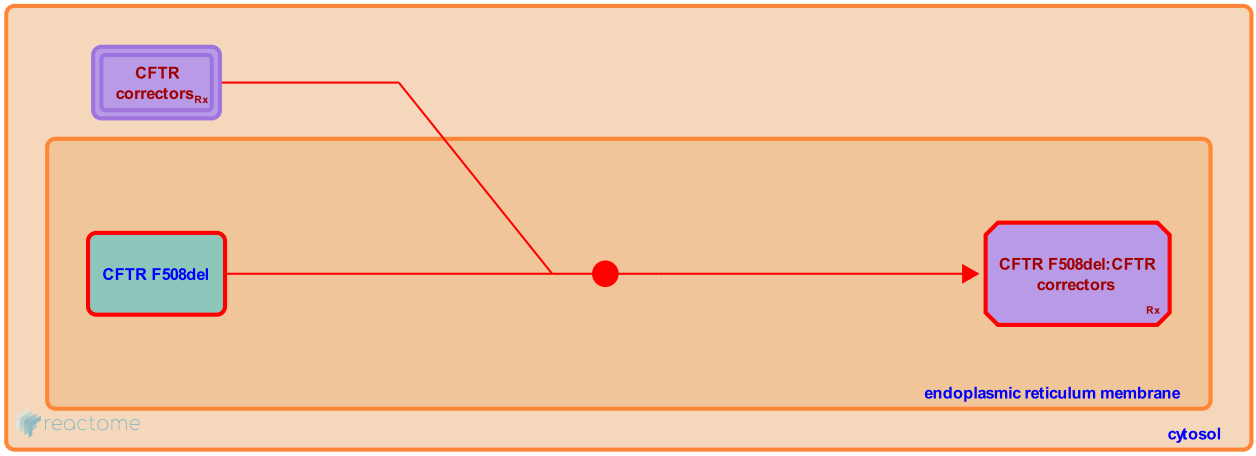
Location: Defective CFTR causes cystic fibrosis

Stable identifier: R-HSA-9700266

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol

Diseases: cystic fibrosis



Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR is a chloride channel in the apical membrane of epithelial cells where it functions to maintain salt and fluid homeostasis. CF is the most common autosomal recessive disease in Caucasian populations. It is a life-limiting condition, with respiratory failure secondary to end-stage lung disease as the main cause of mortality. The majority of disease-causing mutations lead to misfolding of CFTR, including the deletion of phenylalanine at position 508, F508del, occurring in around 90% of patient alleles. Misfolding results in a defective channel where the mutant protein is either released to the cell surface, where it displays dysfunctionality, or is retained in the ER and translocated into the cytosol for degradation by the proteasome.

CFTR correctors have been developed that rescue misfolded mutant CFTRs from the ER that can then translocate to the cell surface to allow any mutant to gain functionality (Mijnders et al. 2017). Small molecule CFTR correctors such as the approved drugs elexacaftor, lumacaftor and tezacaftor and the next-generation corrector bamocaftor have the potential to improve up to 90% of CF patients with the F508del mutation when combined with a CFTR potentiator such as ivacaftor (Keating et al. 2018, Davies et al. 2018, Heijerman et al. 2019).

Literature references

Rowe, SM., McKone, EF., Daines, C., Xuan, F., Young, T., Ramsey, BW. et al. (2018). VX-445-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *N. Engl. J. Med., 379*, 1612-1620. ↗

Van Braeckel, E., Rowe, SM., McKone, EF., Xuan, F., Ramsey, BW., Zhang, Y. et al. (2019). Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet, 394*, 1940-1948. ↗

Mijnders, M., Braakman, I., Kleizen, B. (2017). Correcting CFTR folding defects by small-molecule correctors to cure cystic fibrosis. *Curr Opin Pharmacol, 34*, 83-90. ↗

Horsley, A., Rowe, SM., McKone, EF., Xuan, F., Young, T., Ramsey, BW. et al. (2018). VX-659-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *N. Engl. J. Med., 379*, 1599-1611. ↗

Editions

2021-03-25	Authored	Jassal, B.
2021-10-27	Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

RNF5 and RNF185 ubiquitinate CFTR F508del ↗

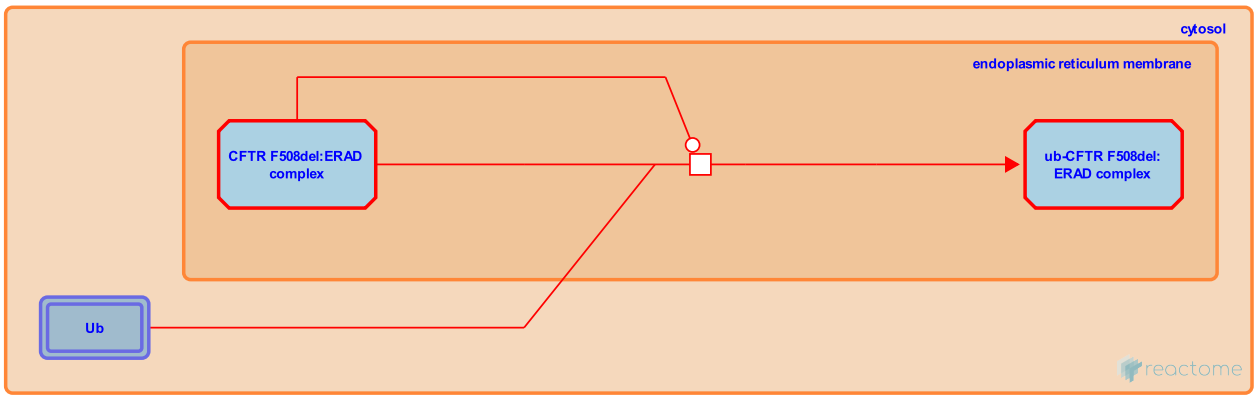
Location: Defective CFTR causes cystic fibrosis

Stable identifier: R-HSA-8866856

Type: transition

Compartments: endoplasmic reticulum membrane

Diseases: cystic fibrosis



RNF5 and RNF185 ubiquitinate CFTR F508del as part of the retrotranslocon that targets the receptor for degradation through the ERAD pathway. Both depletion of the E3 ligases by siRNA and expression of a catalytically inactive form of the enzyme strongly inhibits CFTR degradation (El Khouri et al, 2013; Younger et al, 2006).

Preceded by: CFTR F508del binds components of the ERAD machinery for ubiquitination and degradation

Followed by: VCP-catalyzed ATP hydrolysis promotes the translocation of CFTR F508del into the cytosol

Literature references

El Khouri, E., Toledano, MB., Le Pavec, G., Delaunay-Moisan, A. (2013). RNF185 is a novel E3 ligase of endoplasmic reticulum-associated degradation (ERAD) that targets cystic fibrosis transmembrane conductance regulator (CFTR). *J. Biol. Chem., 288*, 31177-91. ↗

Fan, CY., Ren, HY., Rosser, MF., Younger, JM., Cyr, DM., Turnbull, EL. et al. (2006). Sequential quality-control checkpoints triage misfolded cystic fibrosis transmembrane conductance regulator. *Cell, 126*, 571-82. ↗

Editions

2016-04-02	Authored, Edited	Rothfels, K.
2016-04-23	Reviewed	D'Eustachio, P.

VCP-catalyzed ATP hydrolysis promotes the translocation of CFTR F508del into the cytosol ↗

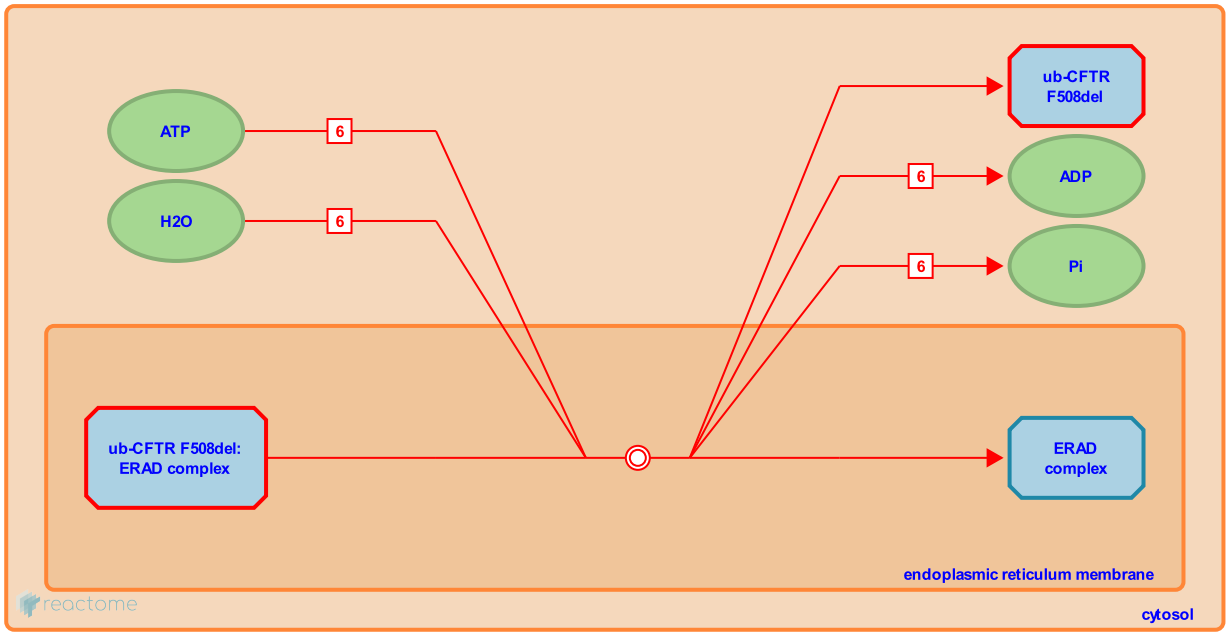
Location: Defective CFTR causes cystic fibrosis

Stable identifier: R-HSA-8866854

Type: dissociation

Compartments: endoplasmic reticulum membrane

Diseases: cystic fibrosis



Retrotranslocation of the misfolded CFTR F508del likely depends on the ERAD ATPase VCP (reviewed in Vembar and Brodsky, 2008; Pranke and Sermet-Gaudelus, 2014).

Preceded by: RNF5 and RNF185 ubiquitinate CFTR F508del

Followed by: CFTR F508del is degraded by the 26S proteasome

Literature references

Sermet-Gaudelus, I., Pranke, IM. (2014). Biosynthesis of cystic fibrosis transmembrane conductance regulator. *Int. J. Biochem. Cell Biol., 52*, 26-38. ↗

Vembar, SS., Brodsky, JL. (2008). One step at a time: endoplasmic reticulum-associated degradation. *Nat. Rev. Mol. Cell Biol., 9*, 944-57. ↗

Editions

2016-04-02	Authored, Edited	Rothfels, K.
2016-04-23	Reviewed	D'Eustachio, P.

CFTR F508del is degraded by the 26S proteasome ↗

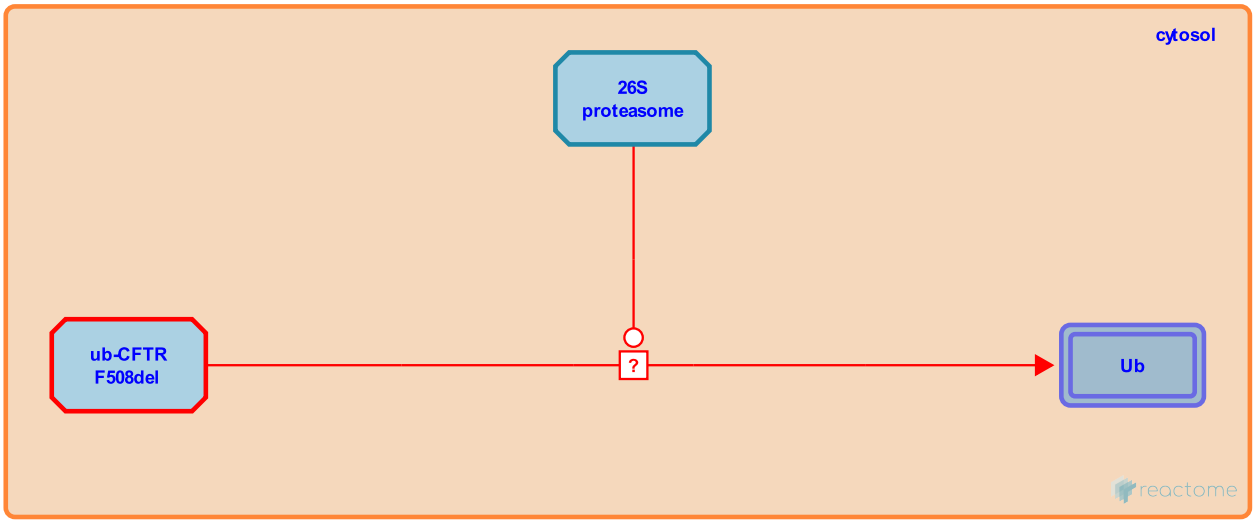
Location: Defective CFTR causes cystic fibrosis

Stable identifier: R-HSA-8866858

Type: uncertain

Compartments: cytosol

Diseases: cystic fibrosis



After VCP-mediated translocation to the cytosol, misfolded CFTR F508del is degraded by the 26S proteasome (El Khouri et al, 2013).

Preceded by: VCP-catalyzed ATP hydrolysis promotes the translocation of CFTR F508del into the cytosol

Literature references

El Khouri, E., Toledano, MB., Le Pavec, G., Delaunay-Moisan, A. (2013). RNF185 is a novel E3 ligase of endoplasmic reticulum-associated degradation (ERAD) that targets cystic fibrosis transmembrane conductance regulator (CFTR). *J. Biol. Chem., 288*, 31177-91. ↗

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2016-04-02	Authored, Edited	Rothfels, K.
2016-04-23	Reviewed	D'Eustachio, P.

Table of Contents