

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.

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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. [↗](#)

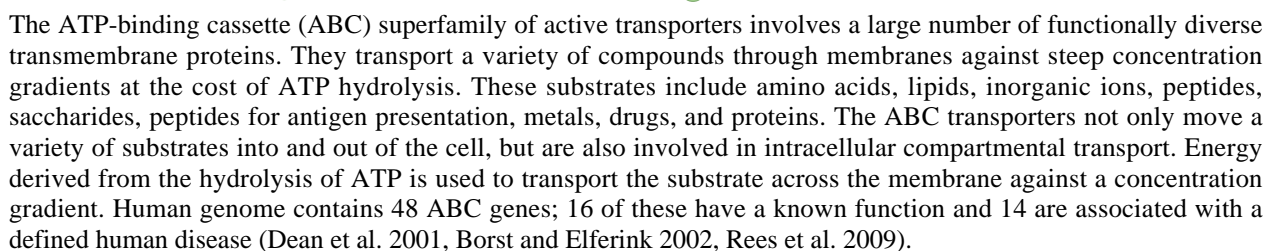
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)

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: 90

This document contains 3 pathways and 14 reactions ([see Table of Contents](#))

Stable identifier: R-HSA-382556



Lewinson, O., Johnson, E., Rees, DC. (2009). ABC transporters: the power to change. *Nat Rev Mol Cell Biol*, 10, 218-27.

Elferink, RO., Borst, P. (2002). Mammalian ABC transporters in health and disease. *Annu Rev Biochem*, 71, 537-92. [↗](#)

2008-11-23	Authored	Gopinathrao, G.
2008-11-29	Edited	Gopinathrao, G.
2008-12-02	Reviewed	Matthews, L.
2011-08-23	Reviewed	D'Eustachio, P.

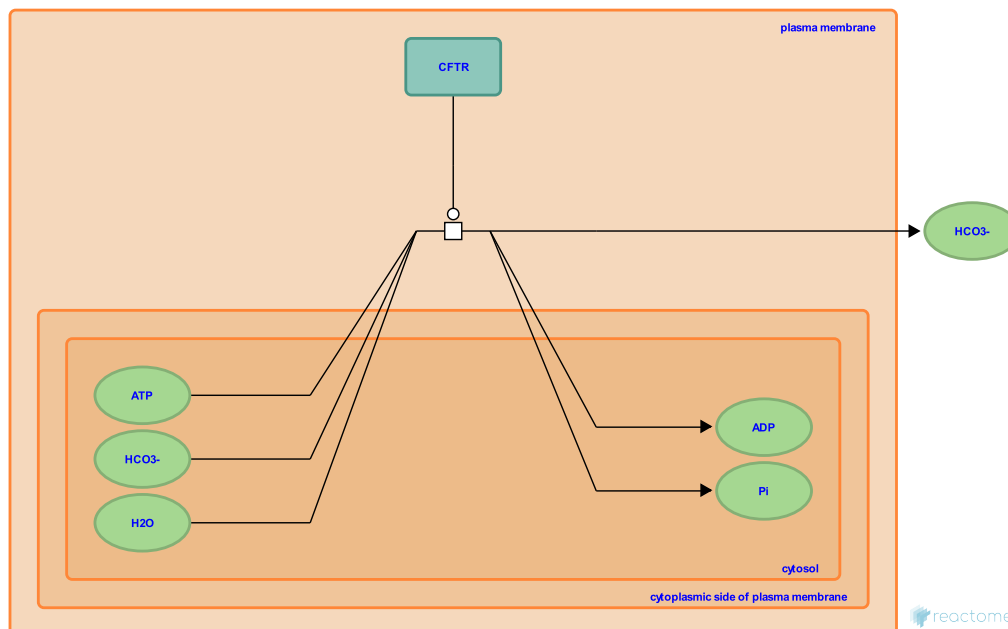
HCO₃⁻ transport through ion channel ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-383190

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Regulation of epithelial chloride flux, which is defective in patients with cystic fibrosis, may be mediated by phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR) by cyclic AMP-dependent protein kinase (PKA) or protein kinase C (PKC). CFTR regulates both HCO₃⁻ secretion and HCO₃⁻ salvage in secretory epithelia.

Preceded by: [CFTR transits to the plasma membrane](#)

Literature references

- Soleimani, M., Burnham, CE. (2001). Na⁺:HCO₃⁻ cotransporters (NBC): cloning and characterization. *J Membr Biol*, 183, 71-84. ↗
- Choi, JY., Lee, MG., Ko, SB., Muallem, S., Pushkin, A., Thomas, PJ. et al. (2002). The cystic fibrosis transmembrane conductance regulator interacts with and regulates the activity of the HCO₃⁻ salvage transporter human Na⁺-HCO₃⁻ cotransport isoform 3. *J Biol Chem*, 277, 50503-9. ↗
- Picciotto, MR., Bertuzzi, G., Greengard, P., Nairn, AC., Cohn, JA. (1992). Phosphorylation of the cystic fibrosis transmembrane conductance regulator. *J Biol Chem*, 267, 12742-52. ↗

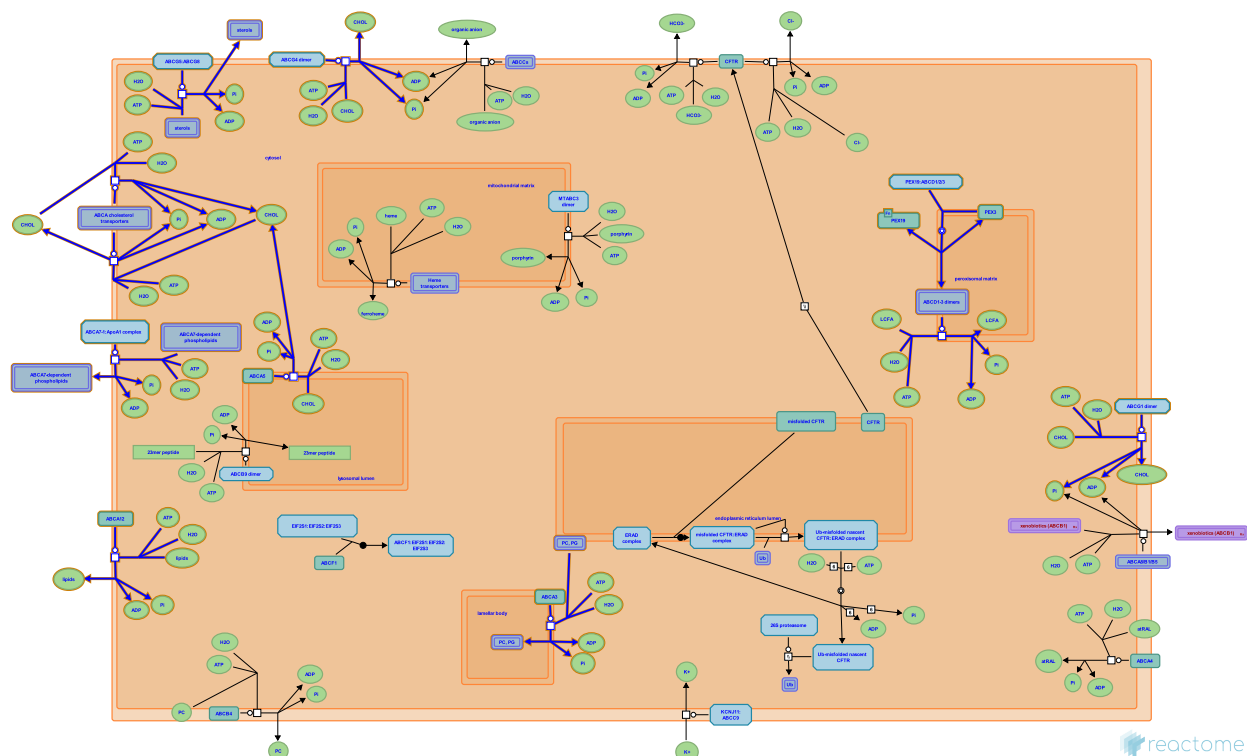
Editions

2008-11-23	Authored	Gopinathrao, G.
2008-11-24	Edited	Gopinathrao, G.
2008-12-02	Reviewed	Matthews, L.

ABC transporters in lipid homeostasis ↗

Location: ABC-family proteins mediated transport

Stable identifier: R-HSA-1369062



A defined subset of the ABC transporter superfamily, the ABCA transporters, are highly expressed in monocytes and macrophages and are regulated by cholesterol flux which may indicate their role in chronic inflammatory diseases (Schmitz and Kaminski 2001, Schmitz et al. 2000). Some D and G members of the ABC transporter family are also important in lipid transport (Voloshyna & Reiss 2011, Morita & Imanaka 2012, Morita et al. 2011).

Literature references

Shimozawa, N., Suzuki, Y., Imanaka, T., Kashiwayama, Y., Morita, M. (2011). ABC subfamily D proteins and very long chain fatty acid metabolism as novel targets in adrenoleukodystrophy. *Curr Drug Targets*, 12, 694-706. ↗

Schmitz, G., Orsó, E., Kaminski, WE. (2000). ABC transporters in cellular lipid trafficking. *Curr Opin Lipidol*, 11, 493-501. ↗

Reiss, AB., Voloshyna, I. (2011). The ABC transporters in lipid flux and atherosclerosis. *Prog. Lipid Res.*, 50, 213-24. ↗

Morita, M., Imanaka, T. (2012). Peroxisomal ABC transporters: structure, function and role in disease. *Biochim. Biophys. Acta*, 1822, 1387-96. ↗

Schmitz, G., Kaminski, WE. (2001). ABC transporters and cholesterol metabolism. *Front Biosci*, 6, D505-14. ↗

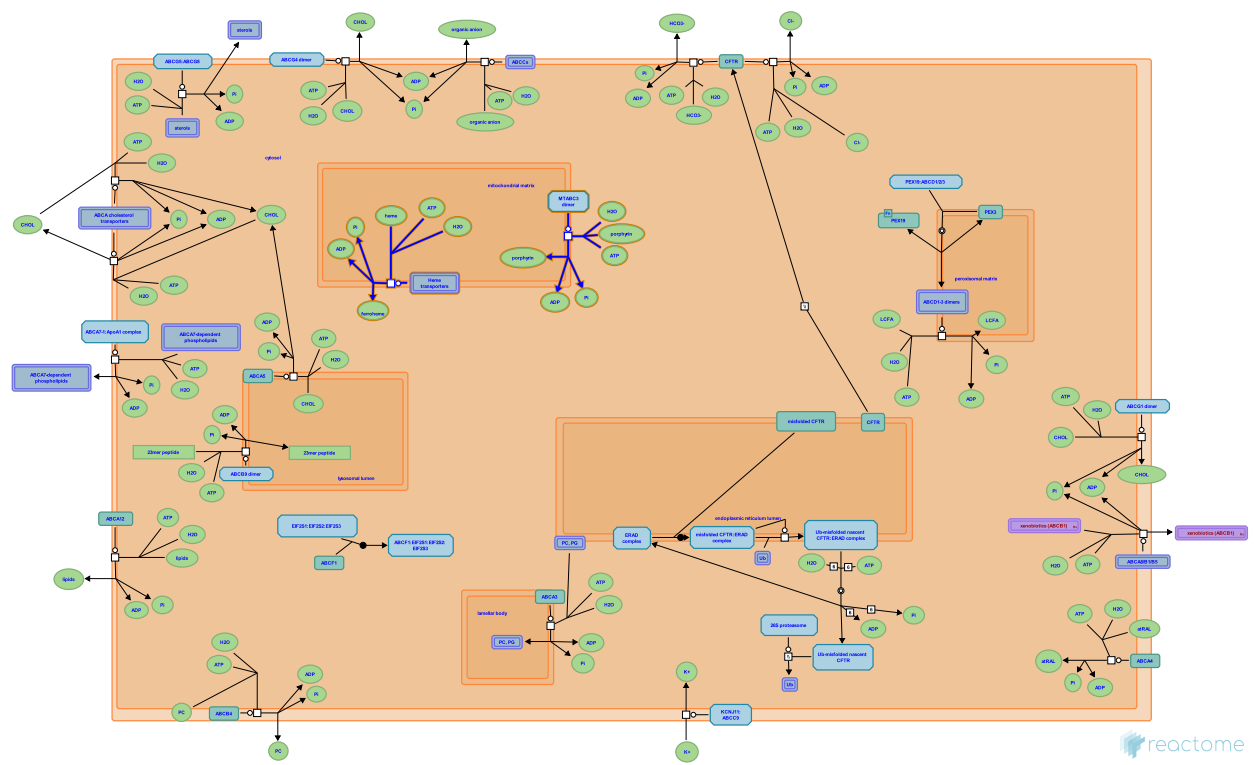
Editions

2011-07-04	Authored, Edited	Jassal, B.
2011-08-23	Reviewed	D'Eustachio, P.

Mitochondrial ABC transporters ↗

Location: ABC-family proteins mediated transport

Stable identifier: R-HSA-1369007



Mammalian ABC transporters are usually found on the plasma membrane and on organelles such as the ER and peroxisome but a small number are also located on the mitochondria. Here they are thought to play roles in heme biosynthesis and iron-sulphur cluster synthesis (Burke & Ardehali 2007).

Literature references

Ardehali, H., Burke, MA. (2007). Mitochondrial ATP-binding cassette proteins. *Transl Res*, 150, 73-80. ↗

Editions

2011-07-04	Authored, Edited	Jassal, B.
2011-08-23	Reviewed	D'Eustachio, P.

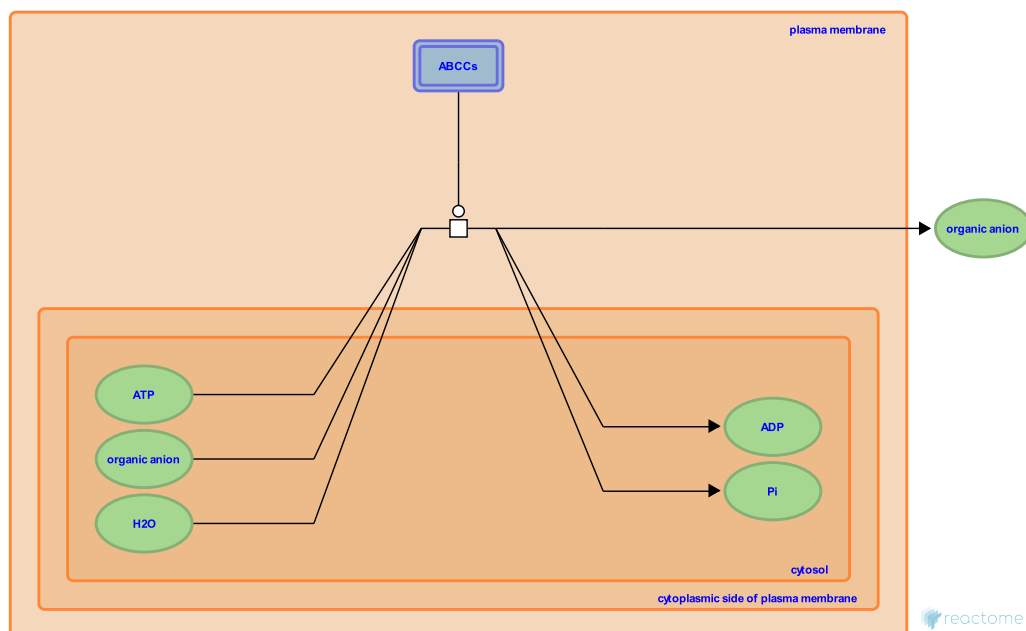
The ABCC family mediates organic anion transport ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-1454916

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The multidrug resistance associated protein (MRPs) subfamily of the ABC transporter family can transport a wide and diverse range of organic anions that can be endogenous compounds and xenobiotics and their metabolites. All human MRPs (except MRP9) can mediate these transport reactions (Deeley et al. 2006). Separately, specific reactions have also been annotated to describe the roles of ABCC4 in platelet dense granule assembly, of ABCC1 in LTC₄ export (an aspect of leukotriene synthesis), and of ABCC3 in bile salt efflux.

Literature references

Deeley, RG., Cole, SP., Westlake, C. (2006). Transmembrane transport of endo- and xenobiotics by mammalian ATP-binding cassette multidrug resistance proteins. *Physiol Rev*, 86, 849-99. ↗

Editions

2011-07-19	Authored, Edited	Jassal, B.
2011-08-23	Reviewed	D'Eustachio, P.

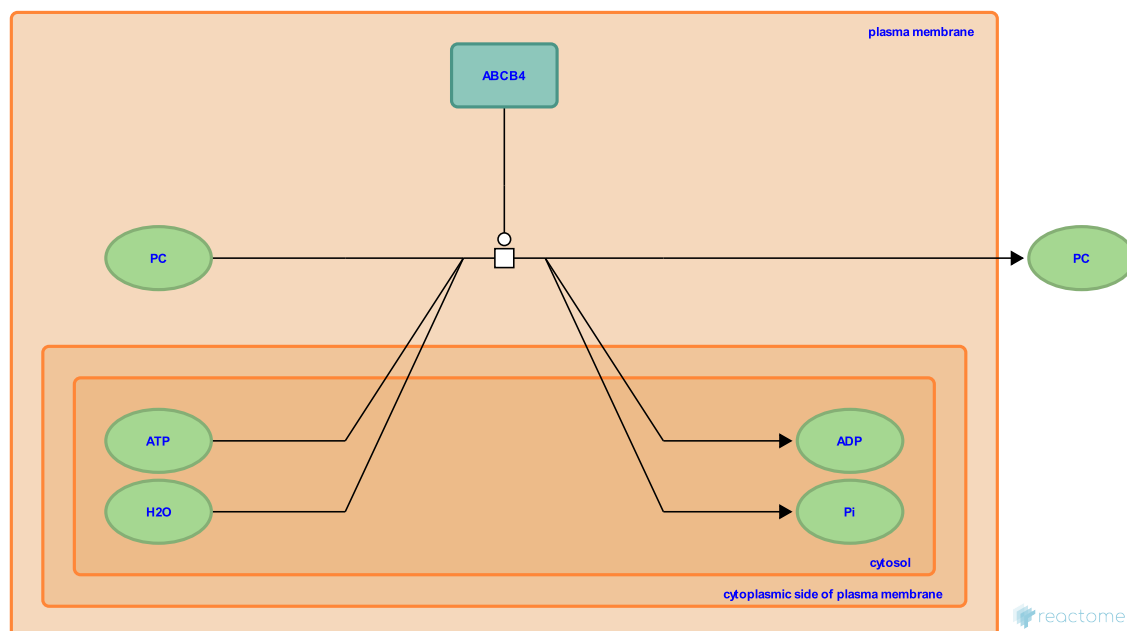
ABCB4 transports PC from plasma membrane to extracellular region ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-5678706

Type: transition

Compartments: plasma membrane, extracellular region



Multidrug resistance protein 3 (ATP-binding cassette sub-family B member 4, ABCB4 aka MDR3) mediates the ATP-dependent export of organic anions and drugs from hepatocytes into the canalicular lumen in the presence of bile salts. ABCB4 is especially important for the export of phospholipids such as phosphatidylcholine (PC) from the plasma membrane of hepatocytes (Morita et al. 2007). Biliary phospholipids associate with bile salts and cholesterol in mixed micelles, thereby reducing the detergent activity and cytotoxicity of bile salts and preventing cholesterol crystallisation. Thus, ABCB4 plays a crucial role in bile formation and lipid homeostasis (Morita & Terada 2014).

Literature references

Kioka, N., Matsuo, M., Morita, SY., Kobayashi, A., Arai, H., Takanezawa, Y. et al. (2007). Bile salt-dependent efflux of cellular phospholipids mediated by ATP binding cassette protein B4. *Hepatology*, 46, 188-99. ↗

Terada, T., Morita, SY. (2014). Molecular mechanisms for biliary phospholipid and drug efflux mediated by ABCB4 and bile salts. *Biomed Res Int*, 2014, 954781. ↗

Editions

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

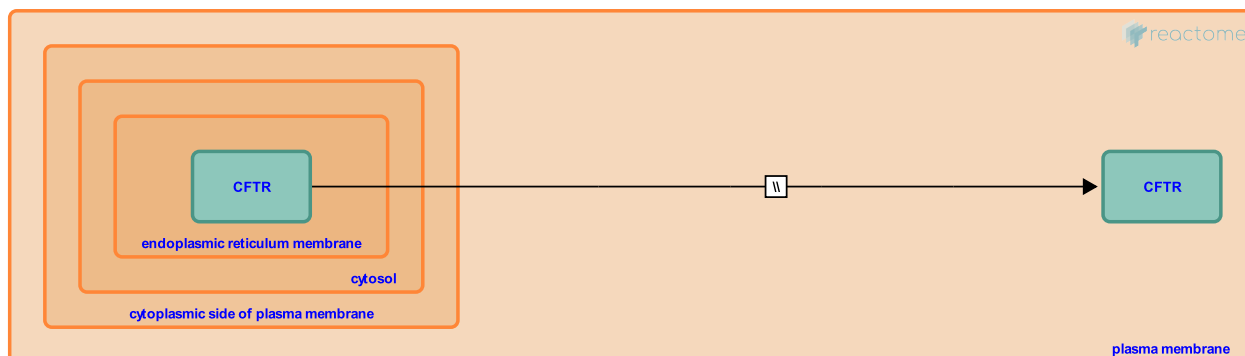
CFTR transits to the plasma membrane ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-8866851

Type: omitted

Compartments: plasma membrane



The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-regulated chloride ion channel that undergoes multiple folding processes and post-translational modifications during its biosynthesis. 60-80% of CFTR protein encoded by the wild-type (WT) gene is successfully modified and transits the secretory system to the plasma membrane. The remaining misfolded protein is targeted for degradation by the ER, lysosomes or autophagy (reviewed in Pranke and Sermet-Gaudelus, 2014)

Followed by: [CFTR transports Cl⁻ from cytosol to extracellular region](#), [HCO₃⁻ transport through ion channel](#)

Literature references

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

Editions

2016-04-02	Authored, Edited	Rothfels, K.
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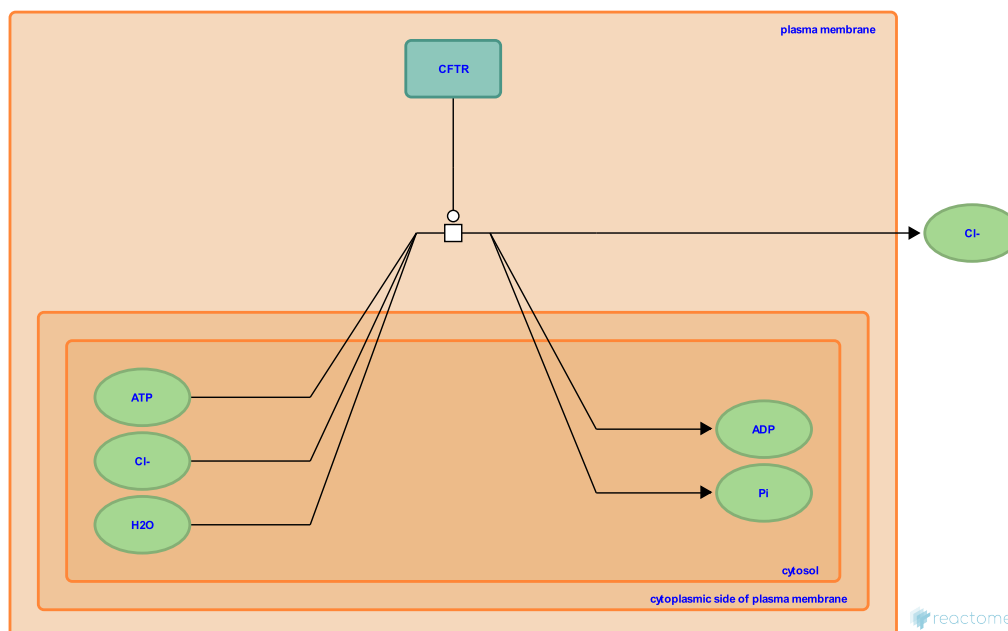
CFTR transports Cl⁻ from cytosol to extracellular region ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-5678863

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



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 homeostasis 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 (Riordan et al. 1999, Ousingsawat et al. 2011).

Preceded by: [CFTR transits to the plasma membrane](#)

Literature references

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

Ousingsawat, J., Kongsuphol, P., Kunzelmann, K., Schreiber, R. (2011). CFTR and TMEM16A are separate but functionally related Cl⁻ channels. *Cell. Physiol. Biochem.*, 28, 715-24. ↗

Editions

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

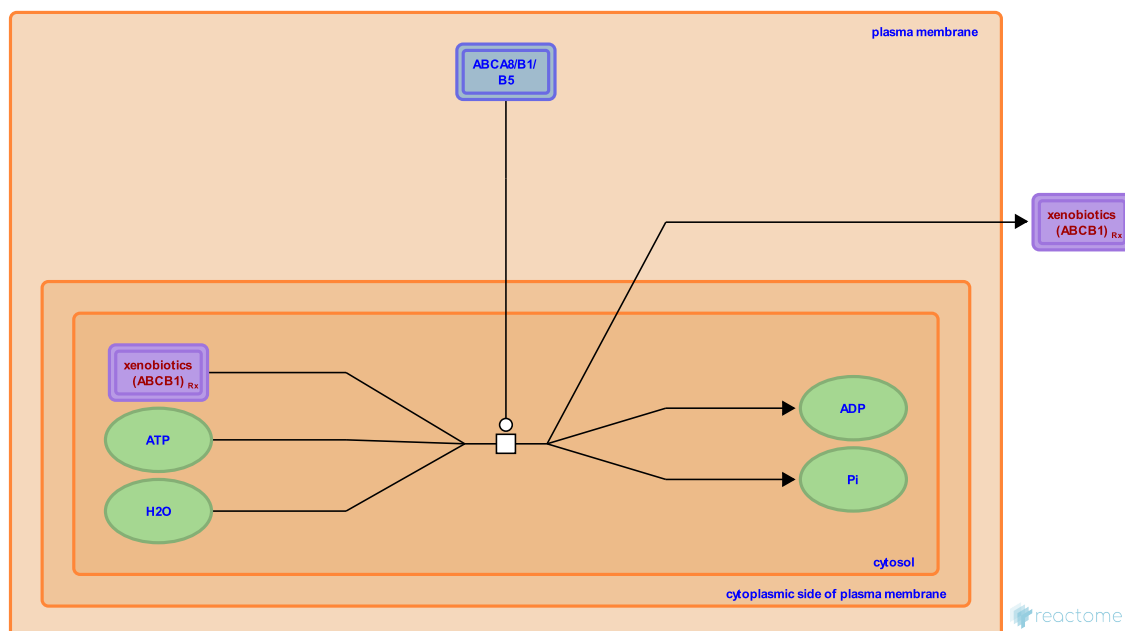
ABCA8,B1,B5 transport xenobiotics from cytosol to extracellular region ↗

Location: ABC-family proteins mediated transport

Stable identifier: R-HSA-1467457

Type: transition

Compartments: cytosol, extracellular region, plasma membrane



Some members of the ABC transporter superfamily are able to mediate the efflux of a broad range of cytotoxic drugs from cells, leading to the name multidrug resistance (MDR) proteins (Seeger and van Veen 2009). The ABCB1 (P-glycoprotein 1 [PGP], multidrug resistance protein 1 [MRP1]) is the most characterised MDR (Shen et al. 1986, Gottesman & Pastan 1988). ABCB5 (Frank et al. 2005) and ABCA8 (Tsuruoka et al. 2002) are newer members of MDRs.

The ABCB1 (also known as MDR1, P-glycoprotein, or PGP) is the best characterized xenobiotic transporter of the ABC transporter family (Shen et al. 1986, Gottesman and Pastan 1988). The ABCB1 gene maps to the chromosomal band 7q21, which is frequently gained or amplified in cancer (Genovese et al. 2017). Transcription of ABCB1 is negatively regulated by TP53 (p53) and positively regulated by CEBPB (C/EBPbeta), JUN (AP-1), NFYB (NF-Y) and YBX1 (YB-1) (Chen and Sikic 2012). ABCB1 is a 12-pass transmembrane protein with two ATP-binding domains (Chen et al. 1986, Gottesman et al. 2002). The question of how many molecules of ATP are hydrolyzed for the full conformational change cycle and export of xenobiotic substrates out of the cell is not settled. The best biochemical evidence is for one molecule of ATP (Shapiro and Ling, 1998; with a review of methods). Structural studies point to the binding of two molecules but do not allow statements about ATP hydrolysis stoichiometry (reviewed in Jones and George, 2020).

Many anti-cancer drugs and anti-inflammatory drugs, as well as some antibiotics, are exported from the cell by ABCB1 (reviewed by Ambudkar et al. 1999, Gottesman et al. 2002).

Anti-cancer drugs that are substrates of ABCB1 include:

- actinomycin D (Horio et al. 1989, Ambudkar et al. 1992, Hill et al. 2013);
- bisantrene (Zhang et al. 1994, Aksentijevich et al. 1996);
- daunorubicin (Horio et al. 1989, Ambudkar et al. 1992);
- docetaxel (Shirakawa et al. 1999);
- doxorubicin (Ueda et al. 1987, Ambudkar et al. 1992);
- etoposide (Pastan et al. 1988, Lincke et al. 1990, Klamt et al. 2008);
- imatinib (Dai et al. 2003);
- irinotecan (Paule et al. 2010, Tagen et al. 2010);
- melphalan (Kühne et al. 2009);
- paclitaxel (Jang et al. 2001);
- temozolomide (Munoz et al. 2015);
- teniposide (Boiocchi et al. 1992);

vinblastine (Ueda et al. 1987, Ambudkar et al. 1992);
vincristine (Horio et al. 1989).

Anti-inflammatory drugs that are substrates of ABCB1 include:

budenoside (Dilger et al. 2004);
colchicine (Ueda et al. 1987);
dexamethasone (Gruol et al. 1999, Yates et al. 2003);
methylprednisolone (Yates et al. 2003, Cuppen et al. 2017);
prednisolone (PREDL) (Karsen et al. 2002, Yates et al. 2003);
prednisone (PREDN) (Dilger et al. 2004).

The presence of 11-, 17-, and 21-hydroxyl groups appears to be a critical determinant for transport efficiency of steroids by the efflux pump ABCB1 (MDR1). Prednisone contains the 17-, and prednisolone both the 17- and 21-hydroxy groups, and both molecules are effectively exported out of cells expressing ABCB1, with reduced intracellular accumulation and toxicity (Yates et al, 2003).

Antibiotics that are substrates of ABCB1 include:

gramicidin D (Lincke et al. 1990, Mechetner and Roninson 1992);
azithromycin (Munić et al. 2010);
erythromycin (Dey et al. 2004, Munić et al. 2010).

Literature references

Eraković Haber, V., Kelnerić, Z., Mikac, L., Munić, V. (2010). Differences in assessment of macrolide interaction with human MDR1 (ABCB1, P-gp) using rhodamine-123 efflux, ATPase activity and cellular accumulation assays. *Eur J Pharm Sci*, 41, 86-95. [↗](#)

Zhang, F., Zhuang, Y., Fraga, CH., Harstead, KE., Stewart, CF., Shen, J. et al. (2010). P-glycoprotein, but not multidrug resistance protein 4, plays a role in the systemic clearance of irinotecan and SN-38 in mice. *Drug Metab Lett*, 4, 195-201. [↗](#)

Swaan, PW., Schuetz, EG., Yates, CR., Yasuda, K., Chang, C., Dalton, JT. et al. (2003). Structural determinants of P-glycoprotein-mediated transport of glucocorticoids. *Pharm. Res.*, 20, 1794-803. [↗](#)

Vo, QD., Gruol, DJ., Zee, MC. (1999). Profound differences in the transport of steroids by two mouse P-glycoproteins. *Biochem. Pharmacol.*, 58, 1191-9. [↗](#)

Gottesman, MM., Lovelace, E., Pastan, I., Ueda, K., Rutherford, AV., Willingham, MC. (1988). A retrovirus carrying an MDR1 cDNA confers multidrug resistance and polarized expression of P-glycoprotein in MDCK cells. *Proc. Natl. Acad. Sci. U.S.A.*, 85, 4486-90. [↗](#)

Editions

2011-08-01	Authored, Edited	Jassal, B.
2011-08-23	Reviewed	D'Eustachio, P.

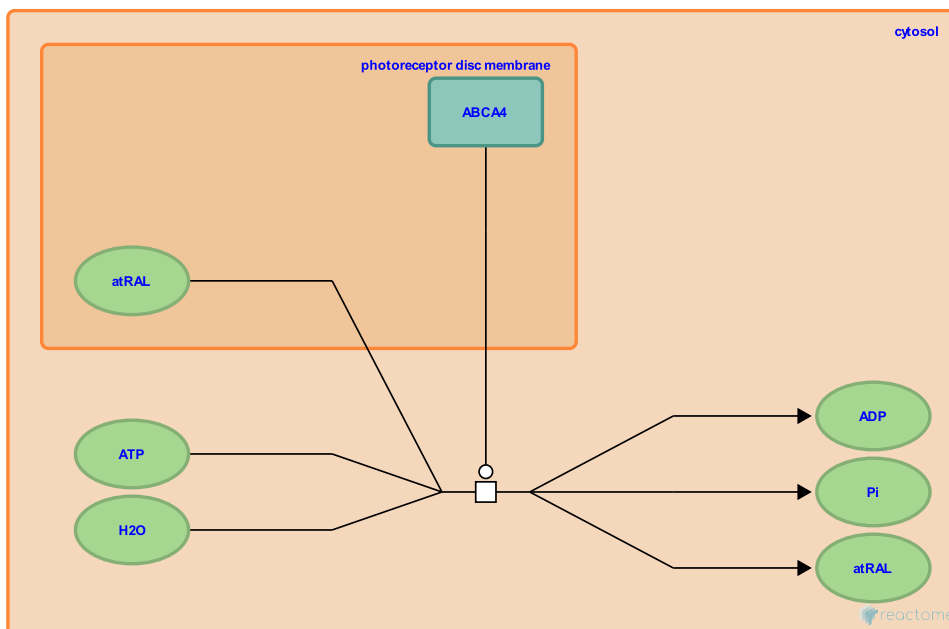
ABCA4 mediates atRAL transport ↗

Location: ABC-family proteins mediated transport

Stable identifier: R-HSA-1467466

Type: transition

Compartments: cytosol, photoreceptor outer segment membrane



Rhodopsin (RHO) is localised to both the disc membrane and the plasma membrane of rod outer segments (ROS). All-trans-retinal (atRAL) released from rhodopsin during the bleaching process, needs to translocate to the cytosol for reduction to all-trans-retinol (atROL) via all-trans-retinol dehydrogenases. Although atRAL can diffuse through membranes unaided, there exists an ABC transporter on disc membranes which may facilitate the transport of excess atRAL. Retinal-specific ATP-binding cassette transporter (ABCA4, ABCR) is the only ABC transporter which mediates the transport of retinoids (Biswas & Biswas 2000). Studies using bovine ABCA4 demonstrates atRAL transport (Sun et al. 1999). Human ABCR was found to be identical to the ABC transporter linked to Stargardt's disease type 1 (STGD1, MIM:248200), a cause of macular degeneration in childhood (Nasonkin et al. 1998).

Literature references

- Nathans, J., Sun, H., Molday, RS. (1999). Retinal stimulates ATP hydrolysis by purified and reconstituted ABCR, the photoreceptor-specific ATP-binding cassette transporter responsible for Stargardt disease. *J Biol Chem*, 274, 8269-81. ↗
- Weber, BH., Nasonkin, I., Illing, M., Schmid, M., Koehler, MR., Molday, RS. (1998). Mapping of the rod photoreceptor ABC transporter (ABCR) to 1p21-p22.1 and identification of novel mutations in Stargardt's disease. *Hum Genet*, 102, 21-6. ↗
- Biswas, EE., Biswas, SB. (2000). The C-terminal nucleotide binding domain of the human retinal ABCR protein is an adenosine triphosphatase. *Biochemistry*, 39, 15879-86. ↗

Editions

2011-08-01	Authored, Edited	Jassal, B.
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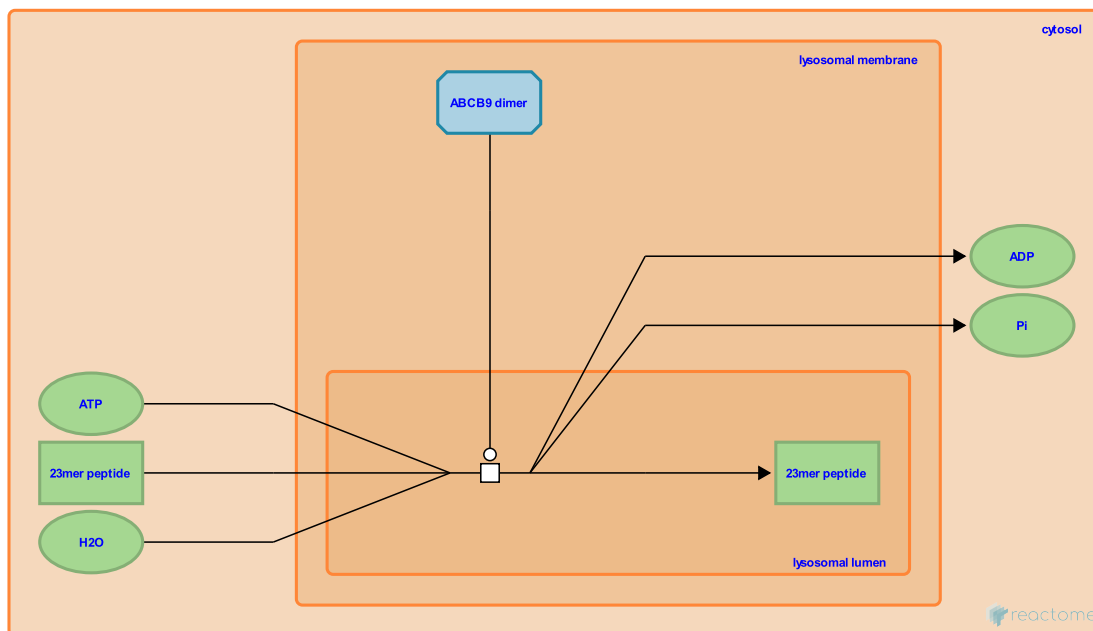
ABCB9 transports peptides from cytosol to lysosomal lumen ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-5223317

Type: transition

Compartments: lysosomal lumen, cytosol, lysosomal membrane



ATP-binding cassette sub-family B member 9 (ABCB9, aka lysosomal ABC transporter associated with antigen processing-like, TAPL) is a homodimeric ATP-dependent low affinity peptide transporter (Wolters et al. 2005), localised on the lysosomal membrane (Zhang et al. 2000). It is able to transport a broad spectrum of peptides (from 6mer up to at least 59mer peptides, optimum of 23mers) from the cytosol to the lysosomal lumen. ABCB9 favours positively charged, aromatic or hydrophobic residues in the N- and C-terminal positions whereas negatively charged residues and asparagine and methionine residues are not favoured (Wolters et al. 2005, Demirel et al. 2007, Zhao et al. 2008). The reaction described here shows the transport of the optimum 23mer peptide.

Literature references

- Appel, S., Grünebach, F., Tampé, R., Brossart, P., Abele, R., Kalinke, U. et al. (2007). Identification of a lysosomal peptide transport system induced during dendritic cell development. *J. Biol. Chem.*, 282, 37836-43. ↗
- Tampé, R., Abele, R., Wolters, JC. (2005). Selective and ATP-dependent translocation of peptides by the homodimeric ATP binding cassette transporter TAP-like (ABCB9). *J. Biol. Chem.*, 280, 23631-6. ↗
- Ling, V., Childs, S., Hui, D., Zhang, W., Dorovini-Zis, K., Liu, L. et al. (2000). Characterization of ABCB9, an ATP binding cassette protein associated with lysosomes. *J. Biol. Chem.*, 275, 23287-94. ↗
- Tampé, R., Haase, W., Abele, R., Zhao, C. (2008). Peptide specificity and lipid activation of the lysosomal transport complex ABCB9 (TAPL). *J. Biol. Chem.*, 283, 17083-91. ↗

Editions

2014-01-06	Authored, Edited, Reviewed	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

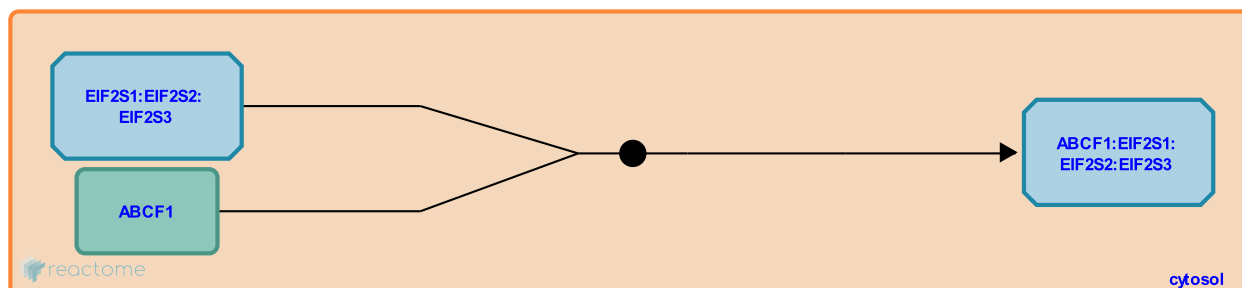
ABCF1 binds EIF2 ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-5227009

Type: binding

Compartments: cytosol



ATP-binding cassette sub-family F member 1 (ABCF1 aka ABC50) is unlike most ABC proteins in that it does not possess membrane-spanning domains. ABCF1 interacts with eukaryotic initiation factor 2 complex (EIF2S1:EIF2S2:EIF2S3), a key player in translation initiation and control and in ribosome regulation. ABCF1 is predominantly located in the cytosol, whereas a smaller amount is also found in the nucleoplasm but not in the nucleolus. Knockout of ABCF1 impaired translation of both cap-dependent and cap-independent reporters, consistent with a positive role for ABCF1 in the function of the EIF2 complex (Paytubi et al. 2008, Paytubi et al. 2009).

Literature references

Lam, YW., Jan, E., Proud, CG., Izquierdo, L., Wang, X., Hunter, MJ. et al. (2009). ABC50 promotes translation initiation in mammalian cells. *J. Biol. Chem.*, 284, 24061-73. ↗

Proud, CG., Morrice, NA., Paytubi, S., Boudeau, J. (2008). The N-terminal region of ABC50 interacts with eukaryotic initiation factor eIF2 and is a target for regulatory phosphorylation by CK2. *Biochem. J.*, 409, 223-31. ↗

Editions

2014-01-09	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

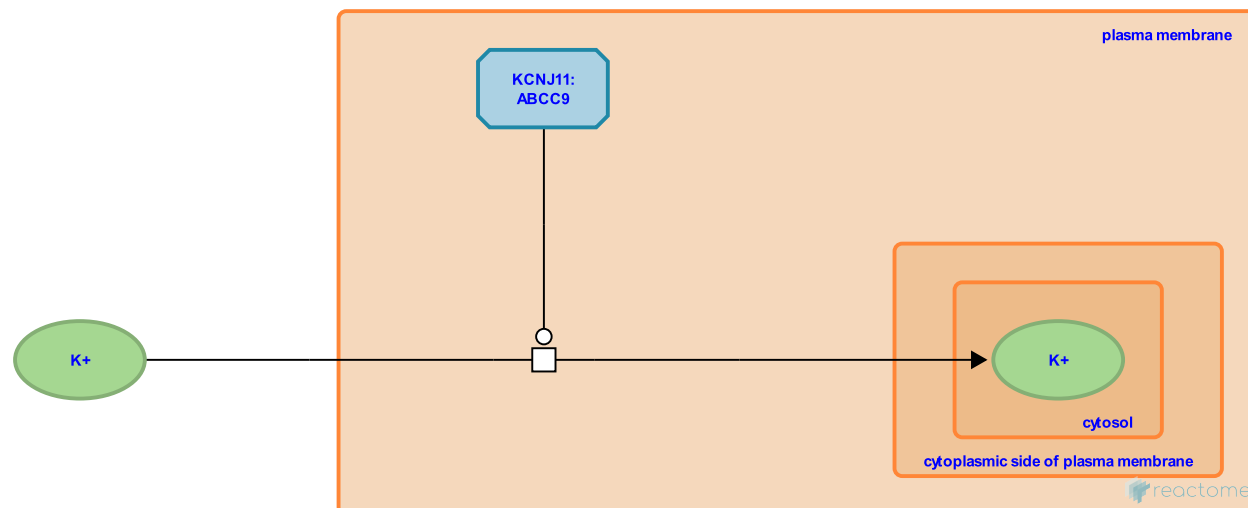
KCNJ11:ABCC9 transports K⁺ from extracellular region to cytosol ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-5678261

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



ATP-sensitive inward rectifier potassium channel 11 (KCNJ11) is an inward rectifier potassium channel, favouring potassium flow into the cell rather than out of it. KCNJ11 can complex with ATP-binding cassette sub-family member 9 (ABCC9) to form cardiac and smooth muscle-type K⁺(ATP) channels. KCNJ11 forms the channel pore while ABCC9 is required for activation and regulation (Babenko et al. 1998, Tammaro & Ashcroft 2007).

Literature references

Ashcroft, FM., Tammaro, P. (2007). A mutation in the ATP-binding site of the Kir6.2 subunit of the KATP channel alters coupling with the SUR2A subunit. *J. Physiol. (Lond.)*, 584, 743-53. ↗

Bryan, J., Gonzalez, G., Aguilar-Bryan, L., Babenko, AP. (1998). Reconstituted human cardiac KATP channels: functional identity with the native channels from the sarcolemma of human ventricular cells. *Circ. Res.*, 83, 1132-43. ↗

Editions

2015-02-23	Authored, Edited	Jassal, B.
2015-04-28	Reviewed	Moitra, K.

CFTR binds components of the ERAD machinery for ubiquitination and degradation

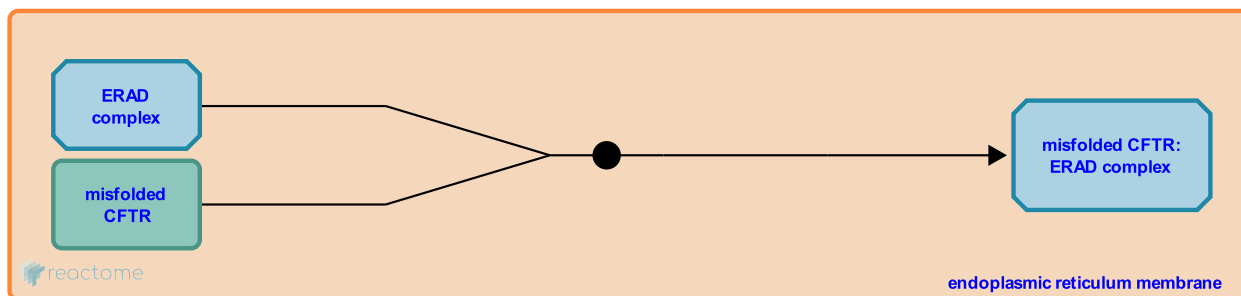


Location: ABC-family proteins mediated transport

Stable identifier: R-HSA-8866551

Type: binding

Compartments: endoplasmic reticulum membrane



Up to two thirds of wild-type CFTR is targeted for co-translational degradation by the ERAD pathway due to inefficient folding (Jensen et al, 1995; Ward et al, 1994; Ward et al, 1995; Gelman et al, 2002; Lukacs et al, 1994). Misfolded CFTR is ubiquitinated in the ER by E3 ligases RNF5 and RNF185, likely as part of a multiprotein retrotranslocation complex containing the hexameric ATPase VCP and various scaffolding and structural proteins (reviewed in Vembar and Brodsky, 2008). Consistent with this, RNF185 interacts directly both with CFTR and with other components of the ERAD machinery, including E2 proteins, ERLIN and DERLIN proteins (Younger et al, 2006; El Khouri et al, 2013).

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. [↗](#)

Omura, S., Ward, CL., Kopito, RR. (1995). Degradation of CFTR by the ubiquitin-proteasome pathway. *Cell*, 83, 121-7. [↗](#)

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. [↗](#)

Ward, CL., Kopito, RR. (1994). Intracellular turnover of cystic fibrosis transmembrane conductance regulator. Inefficient processing and rapid degradation of wild-type and mutant proteins. *J. Biol. Chem.*, 269, 25710-8. [↗](#)

Kannegaard, ES., Kopito, RR., Gelman, MS. (2002). A principal role for the proteasome in endoplasmic reticulum-associated degradation of misfolded intracellular cystic fibrosis transmembrane conductance regulator. *J. Biol. Chem.*, 277, 11709-14. [↗](#)

Editions

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

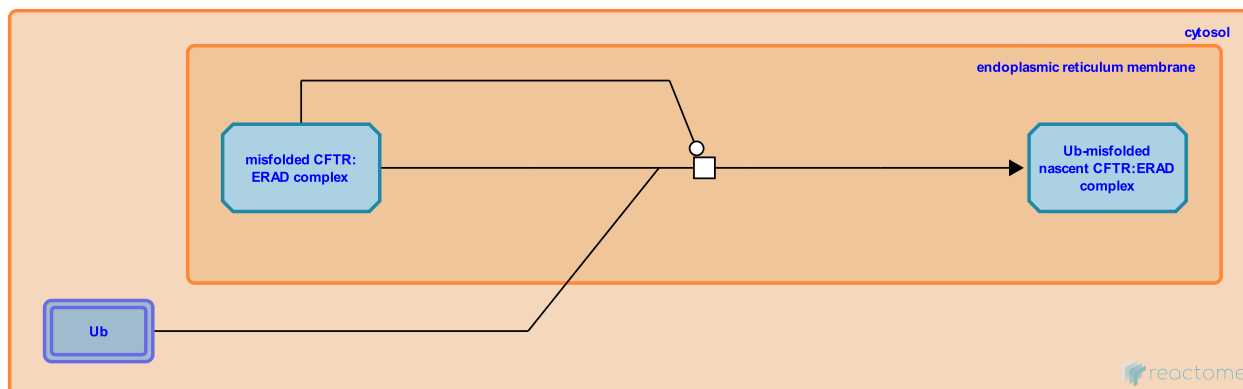
RNF5 and RNF185 ubiquitinate misfolded CFTR ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-8866546

Type: transition

Compartments: endoplasmic reticulum membrane



RNF5 and RNF185 ubiquitinate misfolded CFTR 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).

Followed by: [VCP-catalyzed ATP hydrolysis promotes the translocation of misfolded CFTR 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	Rothfels, K.
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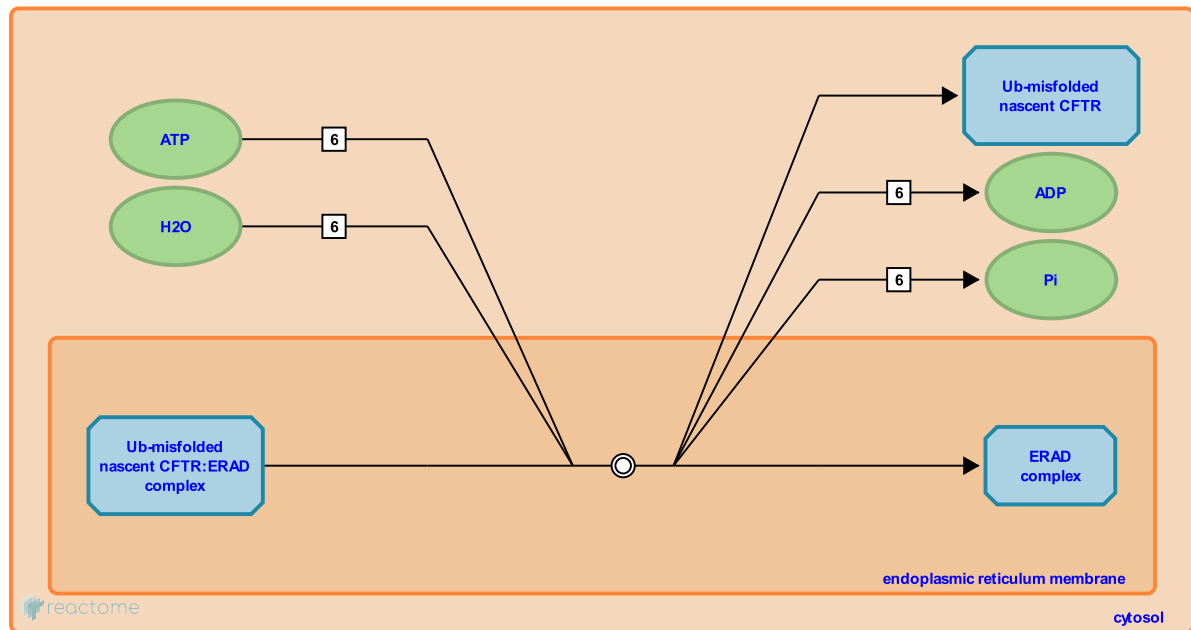
VCP-catalyzed ATP hydrolysis promotes the translocation of misfolded CFTR into the cytosol ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-8866542

Type: dissociation

Compartments: endoplasmic reticulum membrane



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

Preceded by: [RNF5 and RNF185 ubiquitinate misfolded CFTR](#)

Followed by: [misfolded CFTR 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

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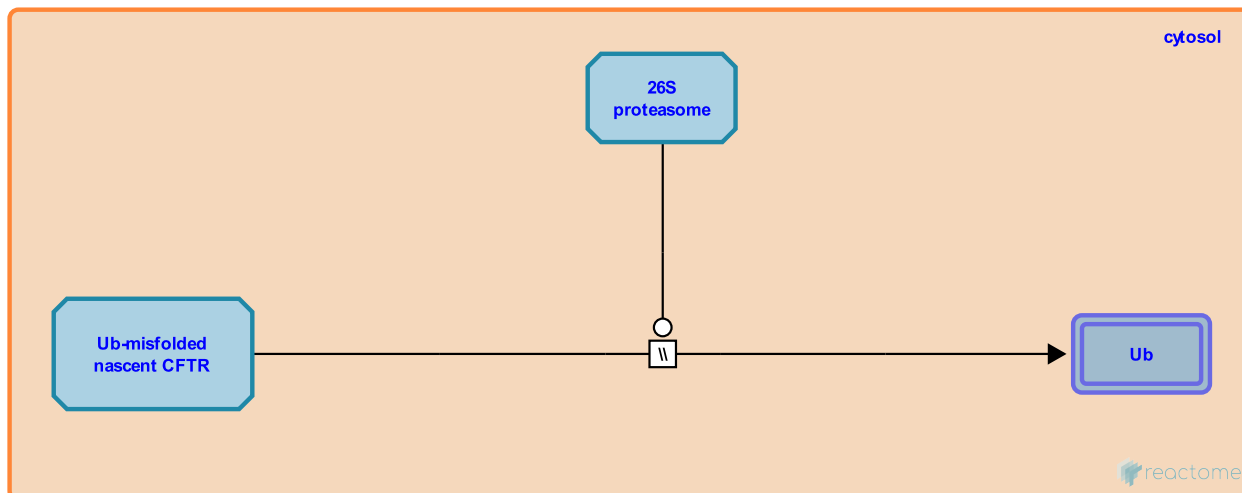
misfolded CFTR is degraded by the 26S proteasome ↗

Location: [ABC-family proteins mediated transport](#)

Stable identifier: R-HSA-8866553

Type: omitted

Compartments: cytosol



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

Preceded by: [VCP-catalyzed ATP hydrolysis promotes the translocation of misfolded CFTR 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. ↗

Editions

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