ABC-family proteins mediated transport

D'Eustachio, P., Gopinathrao, G., Jassal, B., Matthews, L., Moitra, K., Rothfels, K.

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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.

18/11/2022
**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**


Reactome database release: 82

This document contains 3 pathways and 14 reactions (see Table of Contents)
The ATP-binding cassette (ABC) superfamily of active transporters involves a large number of functionally diverse transmembrane proteins. They transport a variety of compounds through membranes against steep concentration gradients at the cost of ATP hydrolysis. These substrates include amino acids, lipids, inorganic ions, peptides, saccharides, peptides for antigen presentation, metals, drugs, and proteins. The ABC transporters not only move a variety of substrates into and out of the cell, but are also involved in intracellular compartmental transport. Energy derived from the hydrolysis of ATP is used to transport the substrate across the membrane against a concentration gradient. Human genome contains 48 ABC genes; 16 of these have a known function and 14 are associated with a defined human disease (Dean et al. 2001, Borst and Elferink 2002, Rees et al. 2009).

**Literature references**


**Editions**

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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 HCO(3)(-) secretion and HCO(3)(-) salvage in secretory epithelia.

**Preceded by:** CFTR transits to the plasma membrane

**Literature references**


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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


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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**

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.

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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**


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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


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

**Preceded by:** CFTR transits to the plasma membrane

**Literature references**


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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/EBP-beta), 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);
teniposide (Boiocchi et al. 1992);
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) (Karssen 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);
erthyromycin (Dey et al. 2004, Munić et al. 2010).

**Literature references**


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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**


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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**


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https://reactome.org
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).

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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).

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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, ER-LIN and DERLIN proteins (Younger et al, 2006; El Khouri et al, 2013).

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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**


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


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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**


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