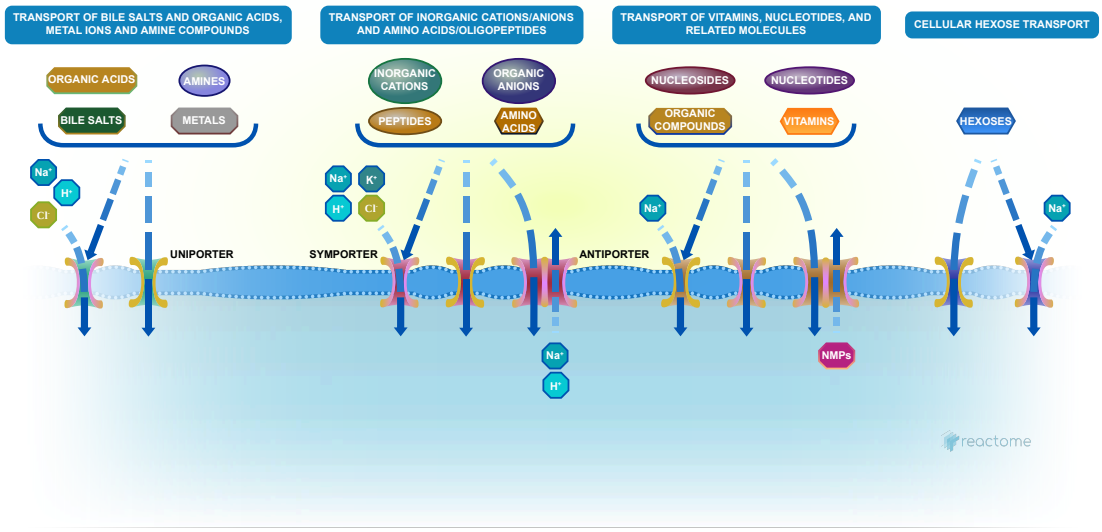
SLC-mediated transmembrane transport



D'Eustachio, P., He, L., Jassal, B., Wright, EM.

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

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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).

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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. ↗

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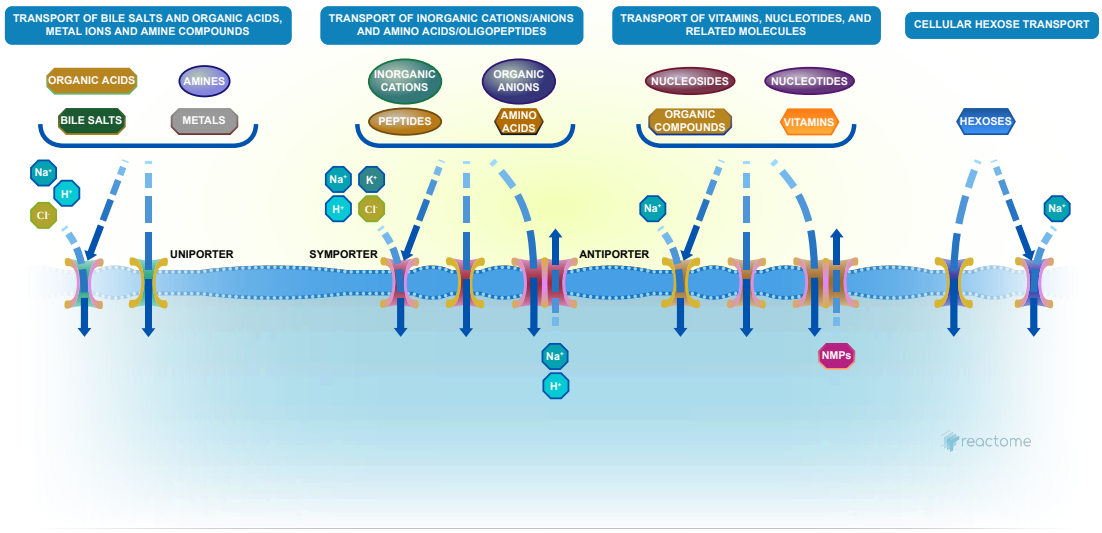
Reactome database release: 88

This document contains 5 pathways (see Table of Contents)

SLC-mediated transmembrane transport ↗

Stable identifier: R-HSA-425407



Proteins with transporting functions can be roughly classified into 3 categories: ATP-powered pumps, ion channels, and transporters. Pumps utilize the energy released by ATP hydrolysis to power the movement of the substrates across the membrane, against their electrochemical gradient. Channels at the open state can transfer the substrates (ions or water) down their electrochemical gradient, at an extremely high efficiency (up to 108 s-1). Transporters facilitate the movement of a specific substrate either against or following their concentration gradient, at a lower speed (about 102 -104 s-1); as generally believed, conformational change of the transporter protein is involved in the transfer process.

According to the Human Genome Organization (HUGO) Gene Nomenclature Committee, all human transporters can be grouped into the solute-carrier (SLC) superfamily (http://www.genenames.org/genefamilies/SLC). Currently, there are 55 SLC families in the superfamily, with a total of at least 362 putatively functional protein-coding genes (Hediger et al. 2004, He et al. 2009; http://www.bioparadigms.org/slc/intro.htm). At least 20-25% amino-acid sequence identity is shared by members belonging to the same SLC family. No homology is shared between different SLC families. While the HUGO nomenclature system by definition only includes human genes, the nomenclature system has been informally extended to include rodent species through the use of lower cases letters (e.g., Slc1a1 denotes the rodent ortholog of the human SLC1A1 gene). And it's worthwhile to mention that pumps, channels and aquaporins are not included in SLC superfamily.

To date, nine SLC gene families (SLC4, SLC5, SLC8, SLC9, SLC12, SLC20, SLC24, SLC26 and SLC34) comprise the group that exclusively transports inorganic cations and anions across membranes. A further eight SLC gene families (SLC1, SLC6, SLC7, SLC16, SLC25, SLC36, SLC38 and SLC43) are involved in the transport of amino acids and oligopeptides (He et al. 2009). Two gene families are responsible for glucose transport in humans. SLC2 (encoding GLUTs) and SLC5 (encoding SGLTs) families mediate glucose absorption in the small intestine, glucose reabsorption in the kidney, glucose uptake by the brain across the blood-brain barrier and glucose release by all cells in the body (Wood & Trayhurn 2003).

SLC transporters are able to transport bile salts, organic acids, metal ions and amine compounds. Myo-Inositol is a precursor to phosphatidylinositols (PtdIns) and to the inositol phosphates (IP), which serve as second messengers and also act as key regulators of many cell functions (Schneider 2015). Mono-, di- and tri-carboxylate transporters mediate the transport of these acids across cellular membranes (Pajor 2006, Morris & Felmlee 2008). Essential metals are transported by metal-transporting proteins, which also control their efflux to avoid toxic build-up (Bressler et al. 2007). The SLC6 gene family encodes proteins that mediate neurotransmitter uptake in the central nervous system (CSN) and peripheral nervous system (PNS), thus terminating a synaptic signal (Chen et al. 2004). Urea transport is particularly important in the process of urinary concentration and for rapid urea equilibrium in non-renal tissues (Olives et al. 1994). Choline uptake is the rate-limiting step in the synthesis of the neurotransmitter acetylcholine. SLC genes SLC5A7 and the SLC44 family encode choline transporters (Traiffort et al. 2005). The

SLC22 gene family of solute carriers function as organic cation transporters (OCTs), cation/zwitterion transporters (OCTNs) and organic anion transporters (OATs). They play important roles in drug absorption and excretion. Substrates include xenobiotics, drugs, and endogenous amine compounds (Koepsell & Endou 2004).

The human SLC5A6 encodes the Na+-dependent multivitamin transporter SMVT (Prasad et al. 1999). SMVT co-transports biotin (vitamin B7), D-Pantothoate (vitamin B5) and lipoic acid into cells with Na+ ions electrogenically. Four SLC gene families encode transporters that play key roles in nucleoside and nucleobase uptake for salvage pathways of nucleotide synthesis, and in the cellular uptake of nucleoside analogues used in the treatment of cancers and viral diseases (He et al. 2009). The human gene SLC33A1 encodes acetyl-CoA transporter AT1 (Kanamori et al. 1997). Acetyl-CoA is transported to the lumen of the Golgi apparatus, where it serves as the substrate of acetyltransferases that O-acetylates sialyl residues of gangliosides and glycoproteins. Nucleotide sugars are used as sugar donors by glycosyltransferases to create the sugar chains for glycoconjugates such as glycoproteins, polysaccharides and glycolipids. The human solute carrier family SLC35 encode nucleotide sugar transporters (NSTs), localised on Golgi and ER membranes, which can mediate the antiport of nucleotide sugars in exchange for the corresponding nucleoside monophosphates (eg. UMP for UDP-sugars) (Handford et al. 2006). Long chain fatty acids (LCFAs) can be used for energy sources and steroid hormone synthesis and regulate many cellular processes such as inflammation, blood pressure, the clotting process, blood lipid levels and the immune response. The SLC27A family encode fatty acid transporter proteins (FATPs) (Anderson & Stahl 2013). The SLC gene family members SLCO1 SLCO2 and SLCO3 encode organic anion transporting polypeptides (OATPs). OATPs are membrane transport proteins that mediate the sodium-independent transport of a wide range of amphipathic organic compounds including bile salts, steroid conjugates, thyroid hormones, anionic oligopeptides and numerous drugs (Hagenbuch & Meier 2004).

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Fukuda, M., Kanamori, A., Sasaki, K., Stallcup, WB., Hirabayashi, Y., Nakayama, J. et al. (1997). Expression cloning and characterization of a cDNA encoding a novel membrane protein required for the formation of O-acetylated ganglioside: a putative acetyl-CoA transporter. *Proc Natl Acad Sci U S A, 94*, 2897-902. ↗

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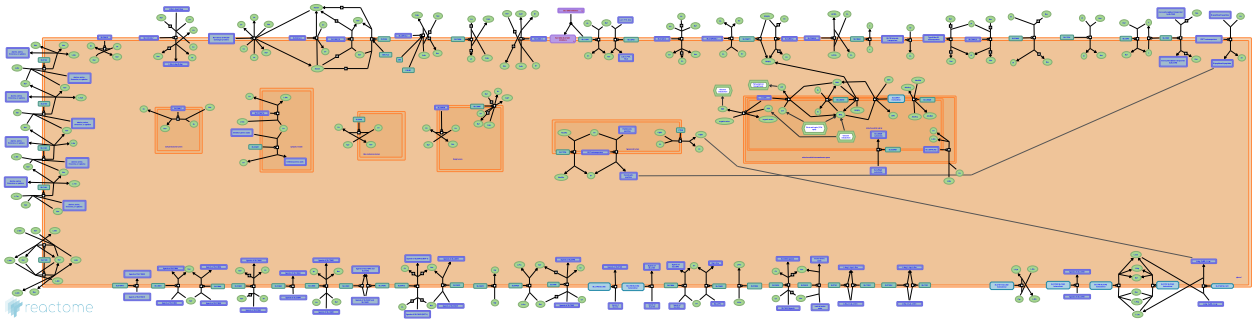
Editions

2009-06-04	Authored, Edited	Jassal, B.
2009-08-24	Reviewed	He, L.
2014-06-09	Revised	Jassal, B.

Transport of inorganic cations/anions and amino acids/oligopeptides ↗

Location: SLC-mediated transmembrane transport

Stable identifier: R-HSA-425393



Teleologically, one might argue that inorganic cation and anion transport would be evolutionarily among the oldest transport functions. Eight families comprise the group that transports exclusively inorganic cations and anions across membranes : SLC4 plays a pivotal role in mediating Na+ - and/or Cl- -dependent transport of basic anions [e.g. HCO3-, (CO3)2-] in various tissues and cell types (in addition to pH regulation, specific members of this family also contribute to vectorial trans-epithelial base transport in several organ systems including the kidney, pancreas, and eye) (Pushkin A and Kurtz I, 2006); SLC8 is a group of Na+/Ca2+ exchangers (SLC8A1 is involved in cardiac contractility) (Quednau BD et al, 2004); SLC24 is a group of Na+/Ca2+ or Na+/K+ exchangers (Altimimi HF and Schnetkamp PP, 2007); SLC9 comprises Na+/H+ exchanger proteins involved in the electroneutral exchange of sodium ion and protons (Orlowski J and Grinstein S, 2004); SLC12 functions as Na+, K+ and Cl- ion electroneutral symporters (Hebert SC et al, 2004); SLC26 is the trans-epithelial multifunctional anion (e.g. sulfate, oxalate, HCO-, Cl-) exchanger family, important in cartilage development, production of thyroid hormone, sound amplification in the cochlea etc (Sindic A et al, 2007; Dorwart MR et al, 2008; Ashmore J, 2008). SLC34 is an important Type II Na+/(HPO4)2- symporter (Forster IC et al, 2006; Virkki LV et al, 2007); SLC20 was originally identified as a viral receptor, and functions as a Type III Na+/(H2PO4)- symporter (Collins JF et al, 2004; Virkki LV et al, 2007). Eight SLC gene families are involved in the transport of amino acids and oligopeptides.

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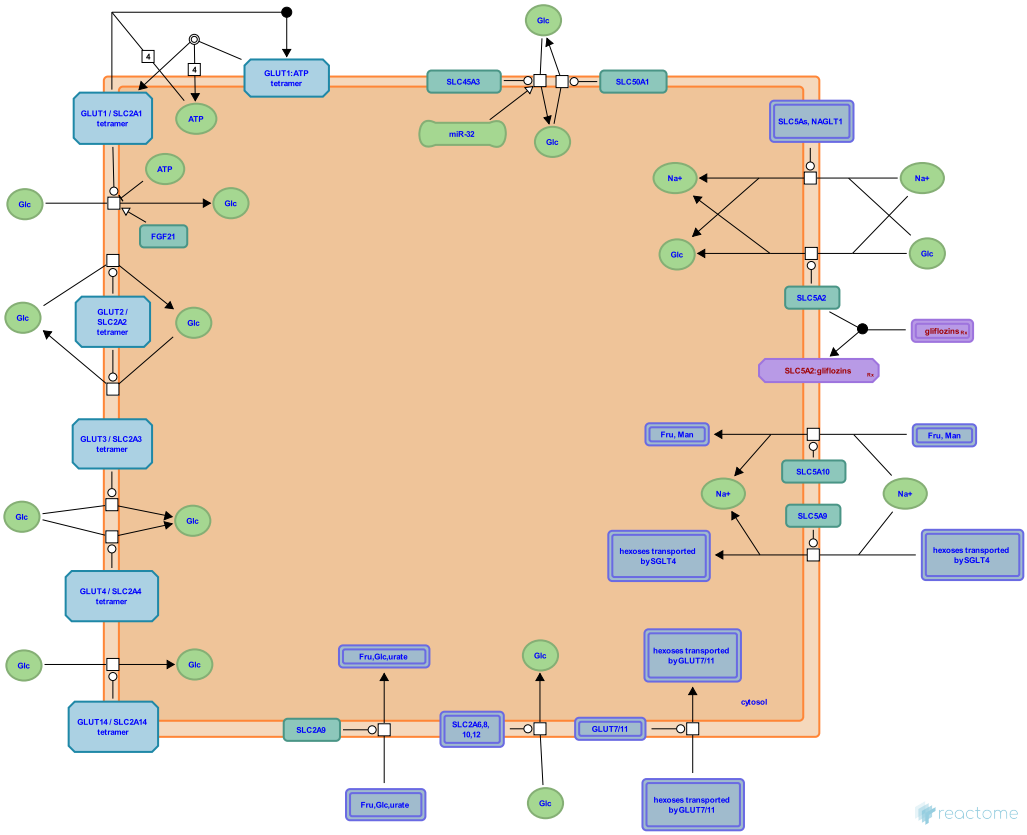
Editions

2009-06-04	Authored, Edited	Jassal, B.
2009-08-24	Reviewed	He, L.

Cellular hexose transport ↗

Location: SLC-mediated transmembrane transport

Stable identifier: R-HSA-189200



Two gene families are responsible for glucose transport in humans. SLC2 (encoding GLUTs) and SLC5 (encoding SGLTs) families mediate glucose absorption in the small intestine, glucose reabsorption in the kidney, glucose uptake by the brain across the blood-brain barrier and glucose release by all cells in the body. Glucose is taken up from interstitial fluid by a passive, facilitative transport driven by the diffusion gradient of glucose (and other sugars) across the plasma membrane. This process is mediated by a family of Na+-independent, facilitative glucose transporters (GLUTs) encoded by the SLC2A gene family (Zhao & Keating 2007; Wood & Trayhurn 2003). There are 14 members belonging to this family (GLUT1-12, 14 and HMIT (H+/myo-inositol symporter)). The GLUT family can be subdivided into three subclasses (I-III) based on sequence similarity and characteristic sequence motifs (Joost & Thorens 2001).

Hexoses, notably fructose, glucose, and galactose, generated in the lumen of the small intestine by breakdown of dietary carbohydrate are taken up by enterocytes lining the microvilli of the small intestine and released from them into the blood. Uptake into enterocytes is mediated by two transporters localized on the lumenal surfaces of the cells, SGLT1 (glucose and galactose, together with sodium ions) and GLUT5 (fructose). GLUT2, localized on the basolateral surfaces of enterocytes, mediates the release of these hexoses into the blood (Wright et al. 2004). GLUT2 may also play a role in hexose uptake from the gut lumen into enterocytes when the lumenal content of monosaccharides is very high (Kellet & Brot-Laroche 2005) and GLUT5 mediates fructose uptake from the blood into cells of the body, notably hepatocytes.

Cells take up glucose by facilitated diffusion, via glucose transporters (GLUTs) associated with the plasma membrane, a reversible reaction. Four tissue-specific GLUT isoforms are known. Glucose in the cytosol is phosphorylated by tissue-specific kinases to yield glucose 6-phosphate, which cannot cross the plasma membrane because of its negative charge. In the liver, this reaction is catalyzed by glucokinase which has a low affinity for glucose (Km about 10 mM) but is not inhibited by glucose 6-phosphate. In other tissues, this reaction is catalyzed by isoforms of hexokinase. Hexokinases are feedback-inhibited by glucose 6-phosphate and have a high affinity for glucose (Km about 0.1 mM). Liver cells can thus accumulate large amounts of glucose 6-phosphate but only when blood glucose concentrations are high, while most other tissues can take up glucose even when blood glucose concentrations are low but cannot accumulate much intracellular glucose 6-phosphate. These differences are consistent with the view that that the liver functions to buffer blood glucose concentrations, while most other tissues

take up glucose to meet immediate metabolic needs.

Glucose 6-phosphatase, expressed in liver and kidney, allows glucose 6-phosphate generated by gluconeogenesis (both tissues) and glycogen breakdown (liver) to leave the cell. The absence of glucose 6-phosphatase from other tissues makes glucose uptake by these tissues essentially irreversible, consistent with the view that cells in these tissues take up glucose for local metabolic use.

Class II facilitative transporters consist of GLUT5, 7, 9 and 11 (Zhao & Keating 2007, Wood & Trayhurn 2003).

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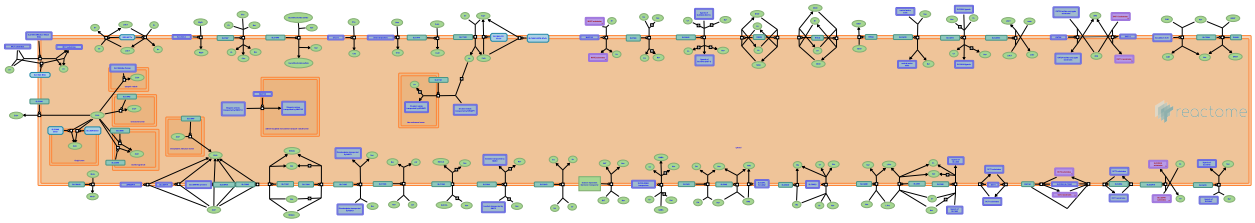
Editions

2006-11-03	Authored	D'Eustachio, P.
2007-01-16	Reviewed	Wright, EM.
2009-08-24	Reviewed	He, L.

Transport of bile salts and organic acids, metal ions and amine compounds ↗

Location: SLC-mediated transmembrane transport

Stable identifier: R-HSA-425366



SLC transporters described in this section transport bile salts, organic acids, metal ions and amine compounds.
Myo-Inositol is a neutral cyclic polyol, abundant in mammalian tissues. It is a precursor to phosphatidylinositols (PtdIns) and to the inositol phosphates (IP), which serve as second messengers and also act as key regulators of many cell functions. Three members of the glucose transporter gene family encode inositol transporters (SLC2A13, SLC5A3 and SLC5A11) (Schneider 2015).
Five human SLC13 genes encode sodium-coupled sulphate, di- and tri-carboxylate transporters typically located on the plasma membrane of mammalian cells (Pajor 2006).
The SLC16A gene family encode proton-linked monocarboxylate transporters (MCT) which mediate the transport of monocarboxylates such as lactate and pyruvate, major energy sources for all cells in the body so their transport in and out of cells is crucial for cellular function (Morris & Felmlee 2008).
The transport of essential metals and other nutrients across tight membrane barriers such as the gastrointestinal tract and blood-brain barrier is mediated by metal-transporting proteins (encoded by SLC11, SLC30, SLC31, SLC39, SLC40 and SLC41). They can also regulate metals by efflux out of cells and cellular compartments to avoid toxic build-up (Bressler et al. 2007).
The SLC6 gene family encodes proteins that mediate neurotransmitter uptake in the central nervous system (CSN) and peripheral nervous system (PNS), thus terminating a synaptic signal. The proteins mediate transport of GABA (gamma-aminobutyric acid), norepinephrine, dopamine, serotonin, glycine, taurine, L-proline, creatine and betaine (Chen et al. 2004).
Carrier-mediated urea transport allows rapid urea movement across the cell membrane, which is particularly important in the process of urinary concentration and for rapid urea equilibrium in non-renal tissues. Two carriers exist in humans, encoded by SLC14A1 and ALC14A2 (Olives et al. 1994).
Choline uptake is the rate-limiting step in the synthesis of the neurotransmitter acetylcholine. SLC genes SLC5A7 and the SLC44 family encode choline transporters ((Okuda & Haga 2000, Traiffort et al. 2005).
The SLC22 gene family of solute carriers function as organic cation transporters (OCTs), cation/zwitterion transporters (OCTNs) and organic anion transporters (OATs). Most of this family are polyspecific transporters. Since many of these transporters are expressed in the liver, kidney and intestine, they play an important role in drug absorption and excretion. Substrates include xenobiotics, drugs, and endogenous amine compounds (Koepsell & Endou 2004).

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Editions

2009-06-04	Authored, Edited	Jassal, B.
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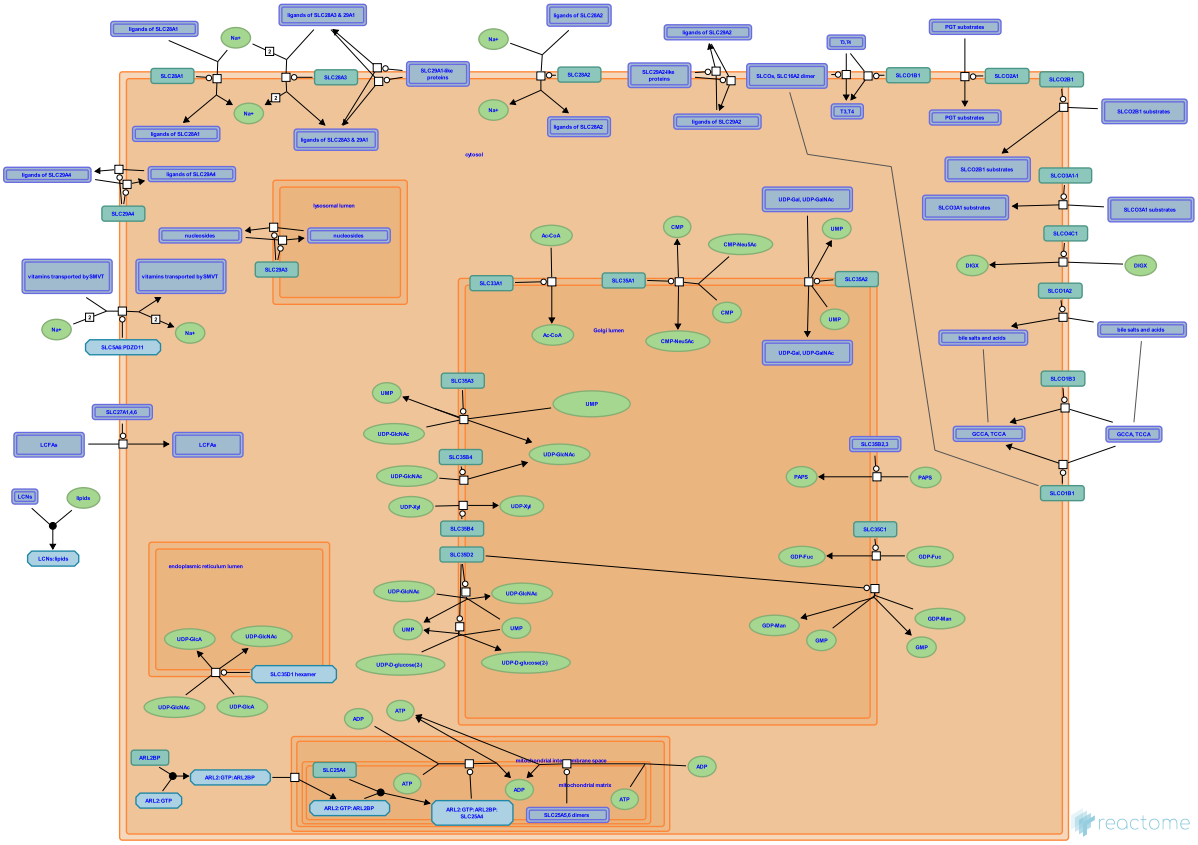
Transport of vitamins, nucleosides, and related molecules ↗

Location: SLC-mediated transmembrane transport

Stable identifier: R-HSA-425397



This section groups the processes mediated by SLC transporters, by which vitamins and cofactors, as well as nucleosides, nucleotides, nucleobases, and related molecules cross lipid bilayer membranes (He et al. 2009).
The human SLC5A6 encodes the Na+-dependent multivitamin transporter SMVT (Prasad et al. 1999). SMVT co-transports biotin (vitamin B7), D-Pantothoate (vitamin B5) and lipoic acid into cells with Na+ ions electrogenically.
Four SLC gene families encode transporters that mediate the movement of nucleosides and free purine and pyrimidine bases across the plasma membrane. These transporters play key roles in nucleoside and nucleobase uptake for salvage pathways of nucleotide synthesis, and in the cellular uptake of nucleoside analogues used in the treatment of cancers and viral diseases (He et al. 2009).
The human gene SLC33A1 encodes acetyl-CoA transporter AT1 (Kanamori et al. 1997). Acetyl-CoA is transported to the lumen of the Golgi apparatus, where it serves as the substrate of acetyltransferases that O-acetylates sialyl residues of gangliosides and glycoproteins.
Nucleotide sugars are used as sugar donors by glycosyltransferases to create the sugar chains for glycoconjugates such as glycoproteins, polysaccharides and glycolipids. Glycosyltransferases reside mainly in the lumen of the Golgi apparatus and endoplasmic reticulum (ER) whereas nucleotide sugars are synthesized in the cytosol. The human solute carrier family SLC35 encode nucleotide sugar transporters (NSTs), localised on Golgi and ER membranes, which can mediate the antiport of nucleotide sugars in exchange for the corresponding nucleoside monophosphates (eg. UMP for UDP-sugars) (Handford et al. 2006).
Long chain fatty acids (LCFAs) can be used for energy sources and steroid hormone synthesis and regulate many cellular processes such as inflammation, blood pressure, the clotting process, blood lipid levels and the immune response. The SLC27A family encode fatty acid transporter proteins (FATPs) (Stahl 2004).
The SLC gene family members SLCO1 SLCO2 and SLCO3 encode organic anion transporting polypeptides (OATPs). OATPs are membrane transport proteins that mediate the sodium-independent transport of a wide range of amphipathic organic compounds including bile salts, steroid conjugates, thyroid hormones, anionic oligopeptides and numerous drugs (Hagenbuch & Meier 2004).

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2014-04-07	Revised	Jassal, B.
2014-06-09	Revised	Jassal, B.

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