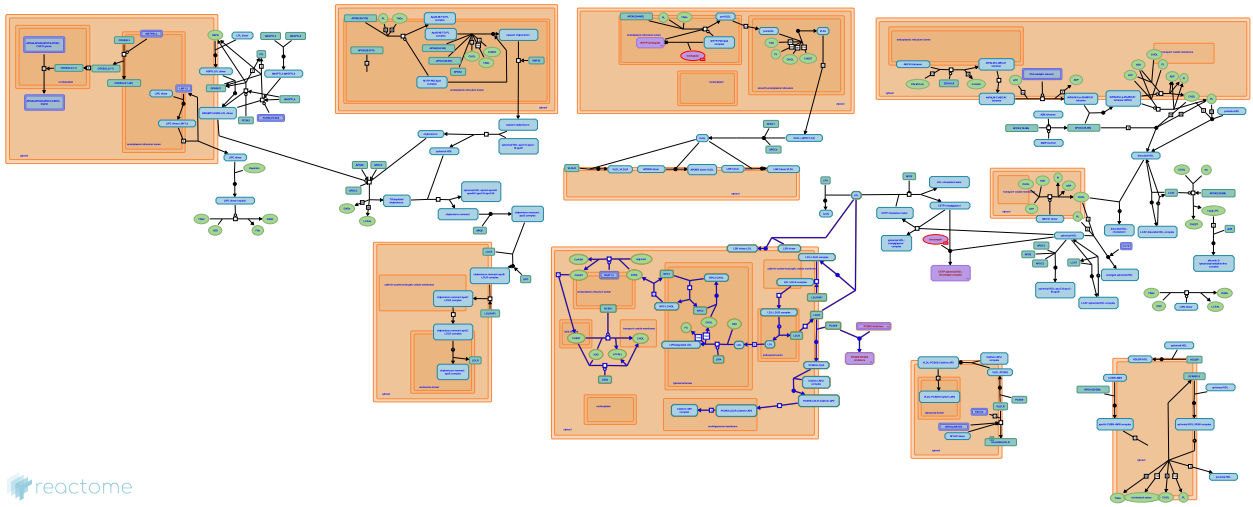
LDL clearance



D'Eustachio, P., Huddart, R., Jassal, B., Matthews, L., Sanchis, A.

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

25/04/2024

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. ↗

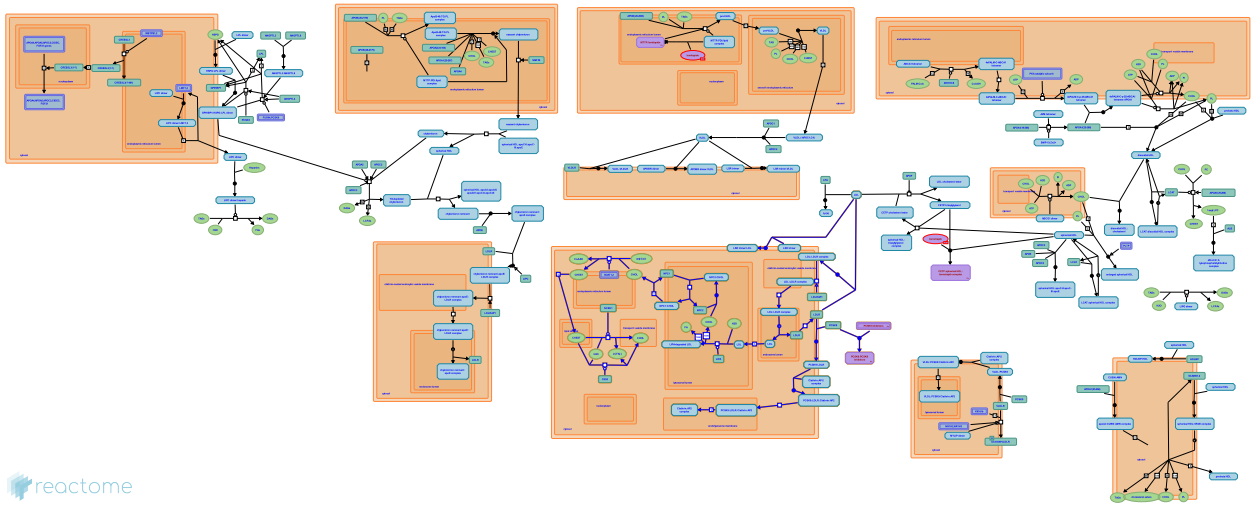
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

LDL clearance

Stable identifier: R-HSA-8964038



LDL (low-density lipoproteins) are complexes of a single molecule of apoprotein B-100 (apoB-100) non-covalently associated with triacylglycerol, free cholesterol, cholesterol esters, and phospholipids.Clearance of LDL from the blood involves binding to LDL receptors associated with coated pits at the cell surface, forming complexes that are internalized and passed via clathrin-coated vesicles to endosomes, where they dissociate. The LDL particles move into lysosomes and are degraded while the LDL receptors are returned to the cell surface. This process occurs in most cell types but is especially prominent in hepatocytes. It plays a major role in returning cholesterol from peripheral tissues to the liver (Hobbs et al. 1990).

Literature references

Hobbs, HH., Goldstein, JL., Brown, MS. (1990). The LDL receptor locus in familial hypercholesterolemia: mutational analysis of a membrane protein. *Annu Rev Genet, 24*, 133-70.

Editions

2007-04-30	Authored, Edited	D'Eustachio, P.
2016-02-10	Authored	Jassal, B.
2016-08-04	Reviewed, Revised	Jassal, B.

LSR trimer binds LDL ↗

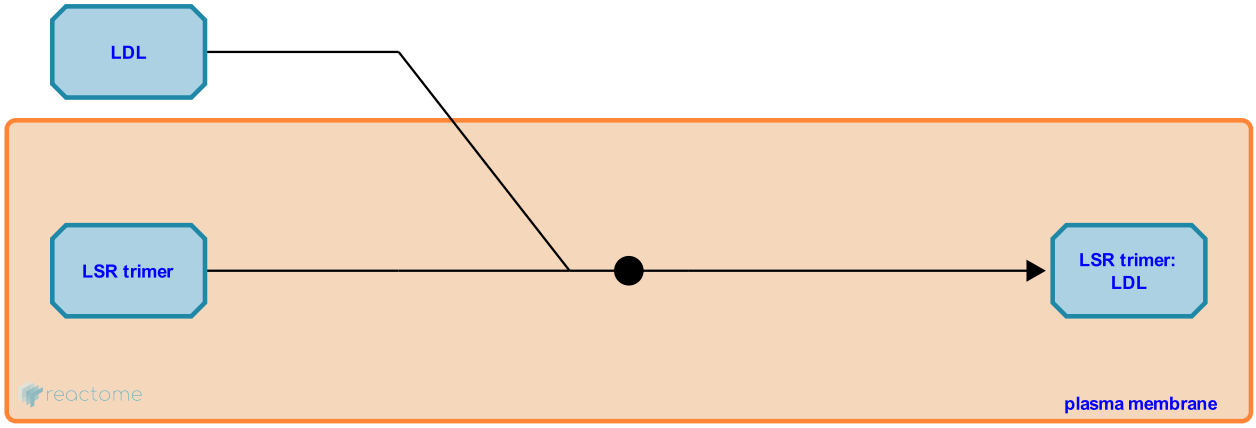
Location: LDL clearance

Stable identifier: R-HSA-8933258

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Lsr trimer binds LDL (Mus musculus)



The human lipolysis-stimulated lipoprotein receptor (LSR, LISCH) probably plays a role in the clearance of triglyceride-rich lipoproteins from blood, allowing their subsequent uptake into cells. Its affinity is highest for those lipoproteins most susceptible to lipolysis such as chylomicrons, LDL and VLDL. Human LSR function is inferred from mouse Lsr expression, functional and gene silencing studies (Yen et al. 1999, Mesli et al. 2004, Yen et al. 2008). Lsr inactivation in mice during embryogenesis resulted in death and indicated expression of Lsr was critical for liver and embryonic development (Mesli et al. 2004). This reaction shows LSR binding LDL.

Literature references

Stenger, C., Notet, V., Bonnard, L., Roitel, O., Pratte, D., Magueur, E. et al. (2008). Lipolysis stimulated lipoprotein receptor: a novel molecular link between hyperlipidemia, weight gain, and atherosclerosis in mice. *J. Biol. Chem. , 283*, 25650-9. ↗

Grosset, JM., Bihain, BE., Guerassimenko, O., André, P., Masson, M., Clossais-Besnard, N. et al. (1999). Molecular cloning of a lipolysis-stimulated remnant receptor expressed in the liver. *J. Biol. Chem., 274*, 13390-8. ↗

Bérard, AM., Darmon, M., Kivlichan, D., Javorschi, S., Mesli, S., Bihain, BE. et al. (2004). Distribution of the lipolysis stimulated receptor in adult and embryonic murine tissues and lethality of LSR-/- embryos at 12.5 to 14.5 days of gestation. *Eur. J. Biochem., 271*, 3103-14. ↗

Editions

2016-08-04	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

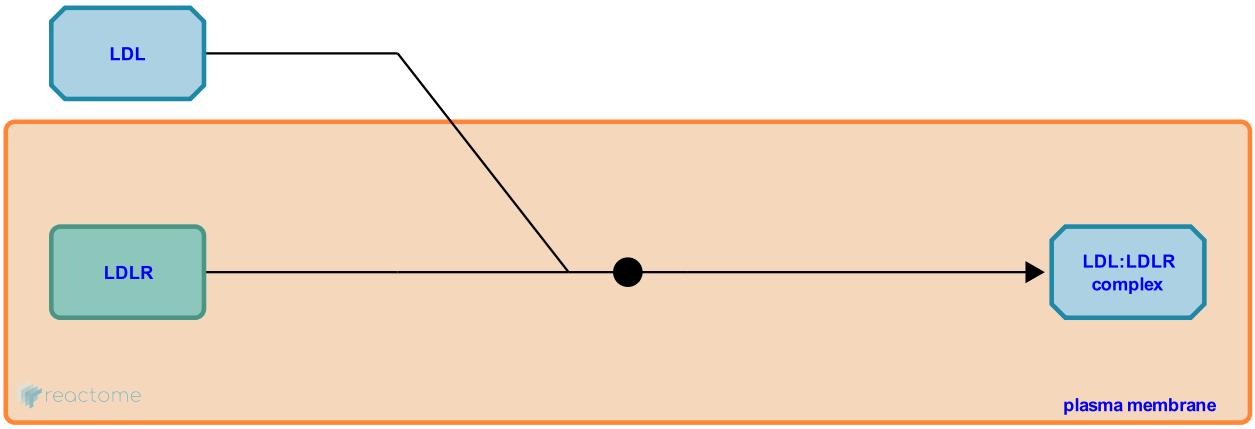
LDL + LDLR => LDL:LDLR complex ↗

Location: LDL clearance

Stable identifier: R-HSA-171122

Type: binding

Compartments: plasma membrane, extracellular region



Low density lipoprotein (LDL) particles associate with LDL receptors (LDLR) at the cell surface (Goldstein et al. 1979). This binding is mediated by the apoprotein B-100 component of the LDL particle, which binds LDLR with 1:1 stoichiometry (van Driel et al. 1989).

Preceded by: LDLR [endosome membrane] => LDLR [plasma membrane]

Followed by: LDL:LDLR complex [plasma membrane] => LDL:LDLR complex [clathrin-coated vesicle] (LDLRAP1-independent)

Literature references

Goldstein, JL., Van Driel, IR., Brown, MS. (1989). Stoichiometric binding of low density lipoprotein (LDL) and monoclonal antibodies to LDL receptors in a solid phase assay. *J Biol Chem, 264*, 9533-8. ↗

Goldstein, JL., Brown, MS., Anderson, RG. (1979). Coated pits, coated vesicles, and receptor-mediated endocytosis. *Nature, 279*, 679-85. ↗

Editions

2006-02-20	Edited	D'Eustachio, P.
2007-04-30	Authored	D'Eustachio, P.

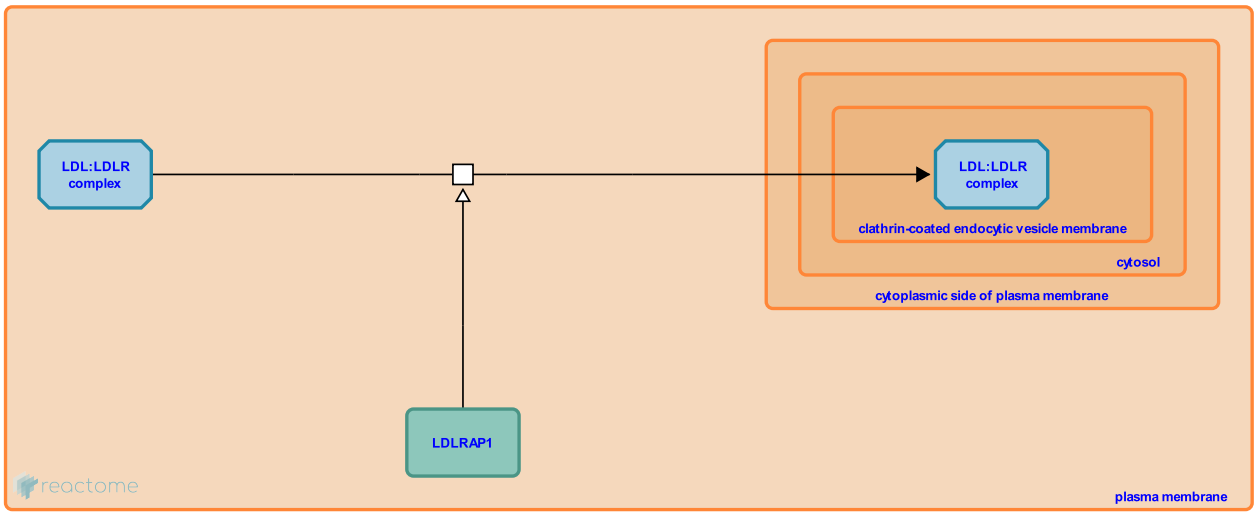
LDL:LDLR complex [plasma membrane] => LDL:LDLR complex [clathrin-coated vesicle] (LDLRAP1-independent) ↗

Location: LDL clearance

Stable identifier: R-HSA-171141

Type: transition

Compartments: plasma membrane



Low density lipoprotein (LDL) particles bound to their receptors (LDLR) in coated pits on the cell surface are taken up into clathrin-coated vesicles (Goldstein et al. 1979). In hepatocytes and lymphocytes, but not in fibroblasts, this process requires the presence of an additional protein, LDLRAP1 (ARH1). In human patients, LDLRAP1 deficiency is associated with hypercholesterolemia, emphasizing the central role of the liver in clearance of circulating LDL in vivo (Eden et al. 2002; Garuti et al. 2005; He et al. 2002; Michaely et al. 2004). In vitro, LDLRAP1 protein binds both to LDLR and to components of the clathrin coat, suggesting that it might play an essential bridging function during the movement of LDL:LDLR complexes into clathrin-coated vesicles. This role has not yet been demonstrated in vivo, however, nor is it clear what might substitute for such a bridging function in fibroblasts.

Preceded by: LDL + LDLR => LDL:LDLR complex

Followed by: LDLR:LDL complex [coated vesicle membrane] => LDLR:LDL complex [endosome membrane]

Literature references

Hobbs, HH., Cohen, JC., Li, WP., Michaely, P., Anderson, RG. (2004). The modular adaptor protein ARH is required for low density lipoprotein (LDL) binding and internalization but not for LDL receptor clustering in coated pits. *J Biol Chem, 279*, 34023-31. ↗

Eden, ER., Patel, DD., Neuwirth, C., Themis, M., Burden, JJ., Naoumova, RP. et al. (2002). Restoration of LDL receptor function in cells from patients with autosomal recessive hypercholesterolemia by retroviral expression of ARH1. *J Clin Invest, 110*, 1695-702. ↗

Hobbs, HH., He, G., Gupta, S., Cohen, JC., Michaely, P., Yi, M. (2002). ARH is a modular adaptor protein that interacts with the LDL receptor, clathrin, and AP-2. *J Biol Chem, 277*, 44044-9. ↗

Goldstein, JL., Brown, MS., Anderson, RG. (1979). Coated pits, coated vesicles, and receptor-mediated endocytosis. *Nature, 279*, 679-85. ↗

Garuti, R., Gerard, RD., Hobbs, HH., Herz, J., Jones, C., Cohen, JC. et al. (2005). The modular adaptor protein autosomal recessive hypercholesterolemia (ARH) promotes low density lipoprotein receptor clustering into clathrin-coated pits. *J Biol Chem, 280*, 40996-1004. ↗

Editions

2006-02-20	Edited	D'Eustachio, P.
2007-04-30	Authored	D'Eustachio, P.

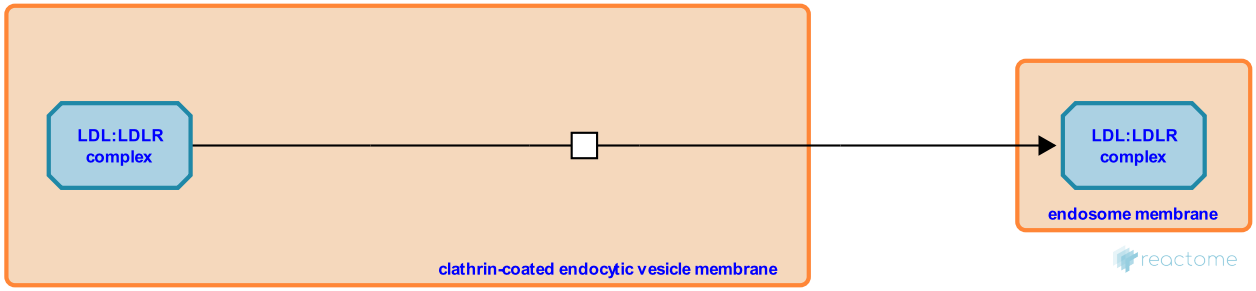
LDLR:LDL complex [coated vesicle membrane] => LDLR:LDL complex [endosome membrane] ↗

Location: LDL clearance

Stable identifier: R-HSA-171059

Type: transition

Compartments: clathrin-coated endocytic vesicle membrane



LDL:LDLR complexes move rapidly from clathrin-coated vesicles to endosomes (Goldstein et al. 1979).

Preceded by: LDL:LDLR complex [plasma membrane] => LDL:LDLR complex [clathrin-coated vesicle] (LDLRAP1-independent)

Followed by: LDLR:LDL complex => LDLR + LDL

Editions

2006-02-20	Edited	D'Eustachio, P.
2007-04-30	Authored	D'Eustachio, P.

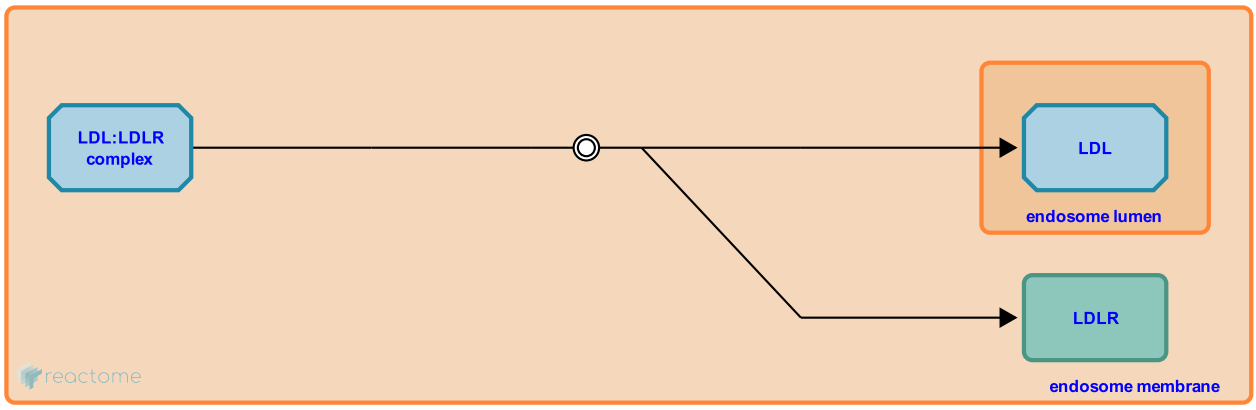
LDLR:LDL complex => LDLR + LDL ↗

Location: LDL clearance

Stable identifier: R-HSA-171106

Type: dissociation

Compartments: endosome membrane, endosome lumen



Dissociation of the LDL:LDLR complex in the early endosome frees the LDL particle to be transferred to lysosomes for degradation while the LDL receptor is returned to the plasma membrane (Goldstein et al. 1979).

Preceded by: LDLR:LDL complex [coated vesicle membrane] => LDLR:LDL complex [endosome membrane]

Followed by: LDL translocates from endosome lumen to lysosome lumen, LDLR [endosome membrane] => LDLR [plasma membrane]

Literature references

Goldstein, JL., Brown, MS., Anderson, RG. (1979). Coated pits, coated vesicles, and receptor-mediated endocytosis. *Nature, 279*, 679-85. ↗

Editions

2006-02-20	Edited	D'Eustachio, P.
2007-04-30	Authored	D'Eustachio, P.

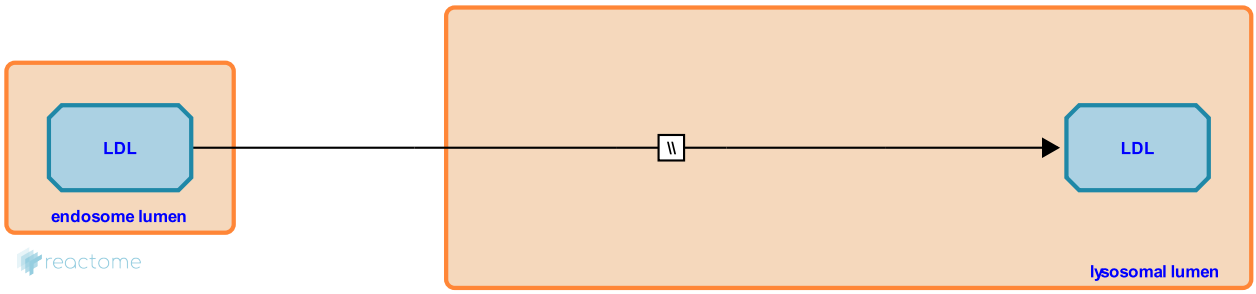
LDL translocates from endosome lumen to lysosome lumen ↗

Location: LDL clearance

Stable identifier: R-HSA-8876366

Type: omitted

Compartments: lysosomal lumen, endosome lumen



Once low-density lipoprotein (LDL) is freed from the LDLR to the endosomal lumen, it translocates to the lysosomal lumen for degradation via a receptor-mediated endocytotic mechanism (Goldstein et al. 1979).

Preceded by: LDLR:LDL complex => LDLR + LDL

Followed by: LIPA hydrolyses sterol esters to sterols and fatty acids

Literature references

Goldstein, JL., Brown, MS., Anderson, RG. (1979). Coated pits, coated vesicles, and receptor-mediated endocytosis. *Nature, 279*, 679-85. ↗

Editions

2016-06-14	Authored, Edited	Jassal, B.
2016-10-19	Reviewed	D'Eustachio, P.

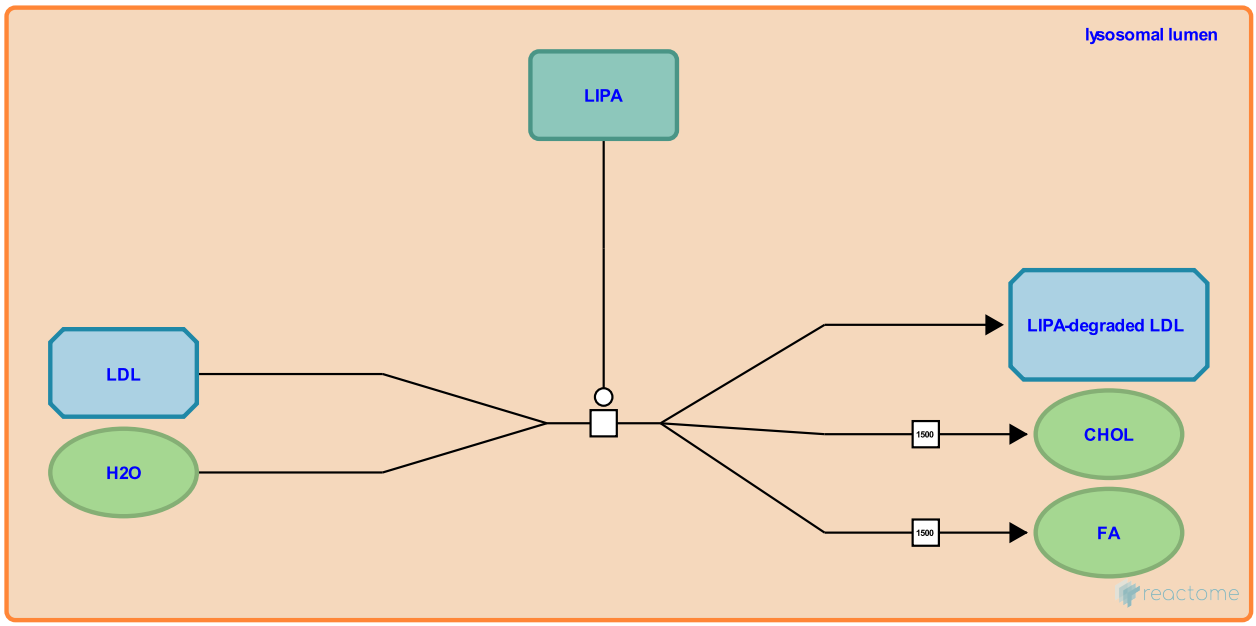
LIPA hydrolyses sterol esters to sterols and fatty acids ↗

Location: LDL clearance

Stable identifier: R-HSA-8865667

Type: transition

Compartments: lysosomal lumen



Lysosomal acid lipase/cholesteryl ester hydrolase (LIPA, aka lysosomal acid lipase, LAL) is structurally related to previously described enteric acid lipases and catalyses the deacylation of triacylglyceryl and cholesteryl ester core lipids of endocytosed low density lipoproteins (LDLs) (Anderson & Sando 1991, Ameis et al. 1994). LIPA is catalytically active in monomeric form. Defects in LIPA can cause Wolman disease (WOD; MIM:278000), a lysosomal lipid storage disorder where cholesteryl esters and triglycerides accumulate in most tissues of the body. WOD occurs in infancy and is nearly always fatal before the age of 1 (Anderson et al. 1994, Du et al. 1998).

Atherosclerosis is characterised by the accumulation of excess cholesterol in the artery wall. In later stages of atherosclerosis, both free cholesterol and cholesteryl ester droplets accumulate within the lysosome. As the cholesterol level increases, it inhibits the proton pumping ability of the vATPases, the pH inside the lysosome increases and renders LIPA catalytically inactive, contributing further to the progression of atherosclerosis (Dubland & Francis 2015).

Preceded by: LDL translocates from endosome lumen to lysosome lumen

Followed by: NPC2 binds CHOL

Literature references

Francis, GA., Dubland, JA. (2015). Lysosomal acid lipase: at the crossroads of normal and atherogenic cholesterol metabolism. *Front Cell Dev Biol, 3*, 3. ↗

Ameis, D., Eckerskorn, C., Merkel, M., Greten, H. (1994). Purification, characterization and molecular cloning of human hepatic lysosomal acid lipase. *Eur. J. Biochem., 219*, 905-14. ↗

Sheriff, S., Du, H., Bezerra, J., Grabowski, GA., Leonova, T. (1998). Molecular and enzymatic analyses of lysosomal acid lipase in cholesteryl ester storage disease. *Mol. Genet. Metab., 64*, 126-34. ↗

Coates, PM., Byrum, RS., Sando, GN., Anderson, RA. (1994). Mutations at the lysosomal acid cholesteryl ester hydrolase gene locus in Wolman disease. *Proc. Natl. Acad. Sci. U.S.A., 91*, 2718-22. ↗

Sando, GN., Anderson, RA. (1991). Cloning and expression of cDNA encoding human lysosomal acid lipase/cholesteryl ester hydrolase. Similarities to gastric and lingual lipases. *J. Biol. Chem., 266*, 22479-84. ↗

Editions

2016-03-23	Authored, Edited	Jassal, B.
2016-07-15	Reviewed	D'Eustachio, P.

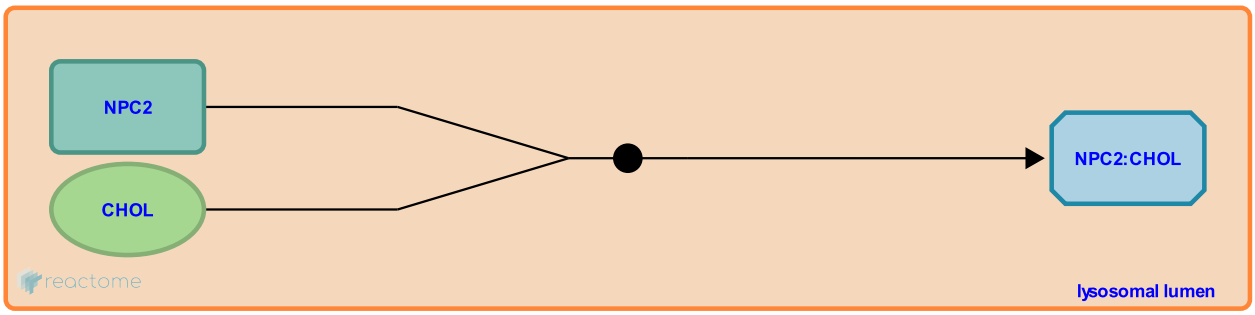
NPC2 binds CHOL ↗

Location: LDL clearance

Stable identifier: R-HSA-8876472

Type: binding

Compartments: lysosomal lumen



In macrophages, the hydrolysis of cholesteryl esters (CHESTs) is the rate-limiting step in the removal of free cholesterol (CHOL) from these cells. CHOL is transported via transport vesicles and can be used for cellular functions or removed from the cell by ABCA1 to create new HDL particles. Accumulation of CHESTs in macrophage foam cells is key to atherosclerotic plaque formation (Dubland & Francis 2015). Exit from lysosomes of CHOL derived from the hydrolysis of CHESTs in low-density lipoproteins (LDLs) requires the concerted effort of two proteins, membrane-bound Niemann-Pick C1 (NPC1) and soluble NPC2. In the first step, NPC2 binds unesterified CHOL that has been released from LDLs in the lumen of lysosomes (Liou et al. 2006).

Preceded by: LIPA hydrolyses sterol esters to sterols and fatty acids, NPC2 transfers CHOL to NPC1

Followed by: NPC2 transfers CHOL to NPC1

Literature references

Francis, GA., Dubland, JA. (2015). Lysosomal acid lipase: at the crossroads of normal and atherogenic cholesterol metabolism. *Front Cell Dev Biol, 3*, 3. ↗

Dixit, SS., Stock, AM., Liou, HL., Tint, GS., Lobel, P., Xu, S. (2006). NPC2, the protein deficient in Niemann-Pick C2 disease, consists of multiple glycoforms that bind a variety of sterols. *J. Biol. Chem., 281*, 36710-23. ↗

Editions

2016-06-15	Authored, Edited	Jassal, B.
2016-10-19	Reviewed	D'Eustachio, P.

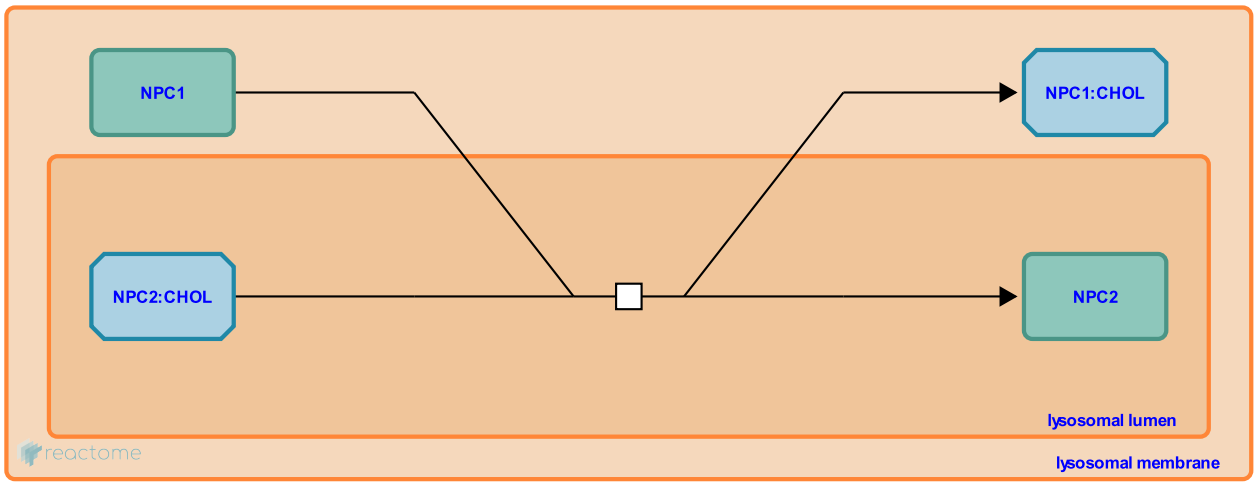
NPC2 transfers CHOL to NPC1 ↗

Location: LDL clearance

Stable identifier: R-HSA-8876484

Type: transition

Compartments: lysosomal lumen, lysosomal membrane



In macrophages, the hydrolysis of cholesteryl esters (CHESTs) is the rate-limiting step in the removal of free cholesterol (CHOL) from these cells. CHOL is transported via transport vesicles and can be used for cellular functions or removed from the cell by ABCA1 to create new HDL particles. Accumulation of CHESTs in macrophage foam cells is key to atherosclerotic plaque formation (Dubland & Francis 2015). Exit from lysosomes of CHOL derived from the hydrolysis of CHESTs in low-density lipoproteins (LDLs) requires the concerted effort of two proteins, membrane-bound Niemann-Pick C1 (NPC1) and soluble NPC2. In the second step, NPC2 transfers CHOL to the CHOL-binding pocket of the N-terminal domain of NPC1 (Infante et al. 2008). During the transfer of CHOL from NPC2 to NPC1, the orientation of CHOL is reversed, allowing insertion of its isooctyl side chain into the outer lysosomal membrane (Kwon et al. 2009).

Preceded by: NPC2 binds CHOL

Followed by: CHOL translocates from lysosome membrane to ER membrane, NPC2 binds CHOL

Literature references

Francis, GA., Dubland, JA. (2015). Lysosomal acid lipase: at the crossroads of normal and atherogenic cholesterol metabolism. *Front Cell Dev Biol, 3*, 3. ↗

Infante, RE., Wang, ML., Goldstein, JL., Kwon, HJ., Radhakrishnan, A., Brown, MS. (2008). NPC2 facilitates bidirectional transfer of cholesterol between NPC1 and lipid bilayers, a step in cholesterol egress from lysosomes. *Proc. Natl. Acad. Sci. U.S.A., 105*, 15287-92. ↗

Deisenhofer, J., Infante, RE., Wang, ML., Goldstein, JL., Kwon, HJ., Abi-Mosleh, L. et al. (2009). Structure of N-terminal domain of NPC1 reveals distinct subdomains for binding and transfer of cholesterol. *Cell, 137*, 1213-24. ↗

Editions

2016-06-15	Authored, Edited	Jassal, B.
2016-10-19	Reviewed	D'Eustachio, P.

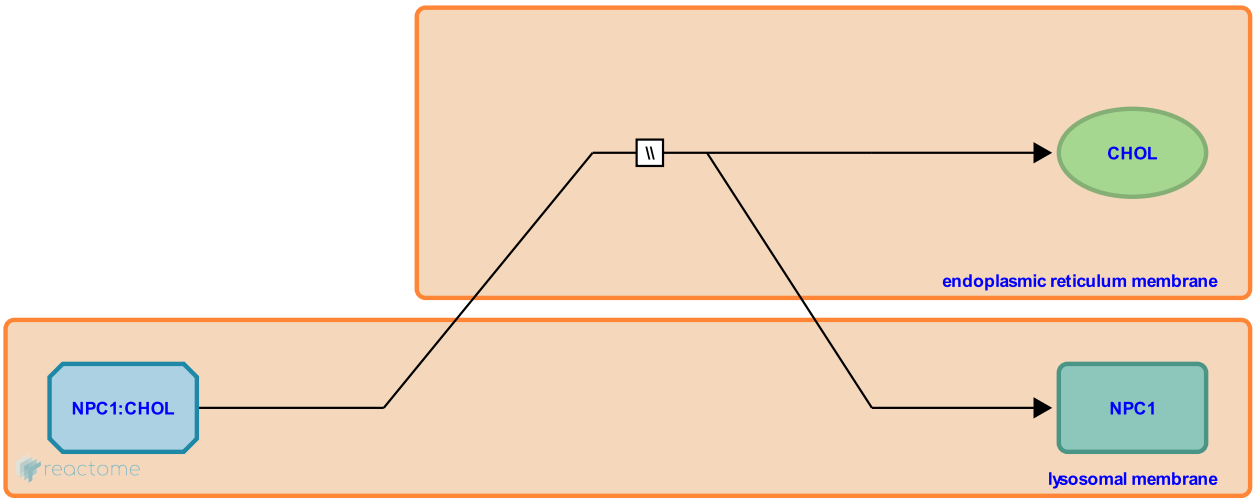
CHOL translocates from lysosome membrane to ER membrane ↗

Location: LDL clearance

Stable identifier: R-HSA-8876485

Type: omitted

Compartments: endoplasmic reticulum membrane, lysosomal membrane



In macrophages, the hydrolysis of cholesteryl esters (CHESTs) is the rate-limiting step in the removal of free cholesterol (CHOL) from these cells. CHOL is transported via transport vesicles and can be used for cellular functions or removed from the cell by ABCA1 to create new HDL particles. Accumulation of CHESTs in macrophage foam cells is key to atherosclerotic plaque formation (Dubland & Francis 2015). CHOL is positioned on the outer membrane of lysosomes and translocates to the ER membrane where it can be re-esterified for storage. The mechanism of translocation is currently unknown (Infante et al. 2008).

Preceded by: NPC2 transfers CHOL to NPC1

Followed by: SOAT1,2 transfer acyl group to CHOL forming CHEST

Literature references

Francis, GA., Dubland, JA. (2015). Lysosomal acid lipase: at the crossroads of normal and atherogenic cholesterol metabolism. *Front Cell Dev Biol, 3*, 3. ↗

Infante, RE., Wang, ML., Goldstein, JL., Kwon, HJ., Radhakrishnan, A., Brown, MS. (2008). NPC2 facilitates bidirectional transfer of cholesterol between NPC1 and lipid bilayers, a step in cholesterol egress from lysosomes. *Proc. Natl. Acad. Sci. U.S.A., 105*, 15287-92. ↗

Editions

2016-06-15	Authored, Edited	Jassal, B.
2016-10-19	Reviewed	D'Eustachio, P.

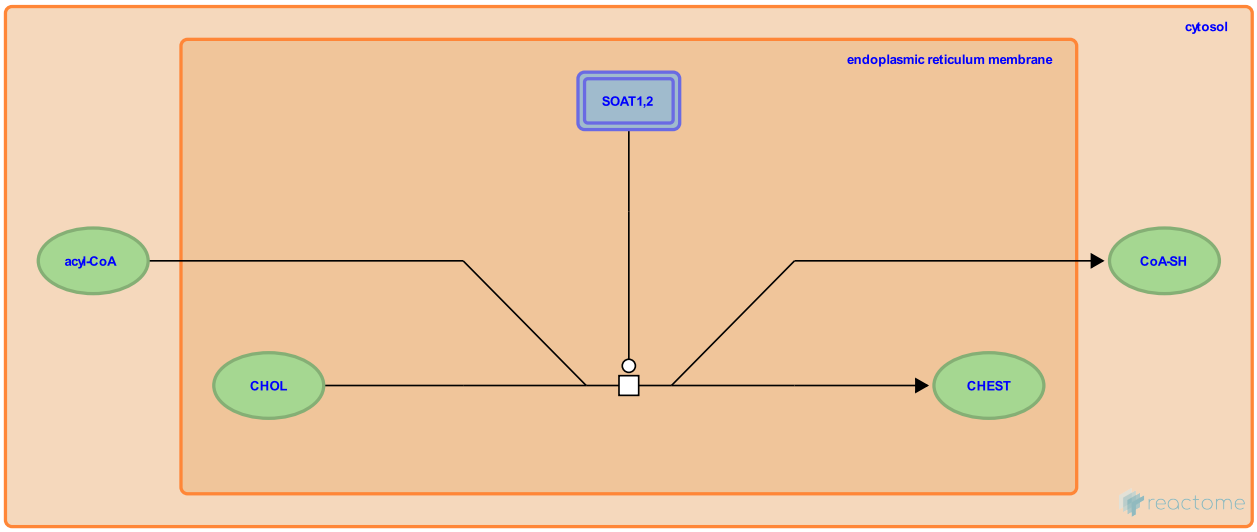
SOAT1,2 transfer acyl group to CHOL forming CHEST ↗

Location: LDL clearance

Stable identifier: R-HSA-8876696

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Excess cellular cholesterol (CHOL) is esterified and stored as cholesteryl ester (CHEST). The conversion is catalysed by the ER membrane-residing sterol O-acyltransferases 1 and 2 (SOAT1 and SOAT 2, aka acyl-coenzyme A:cholesterol acyltransferase 1 and 2, ACAT1 and 2) (Chang et al. 1993, Oelkers et al. 1998, Lin et al. 1999). CHESTs are usually present at low levels in most cells but chronic accumulation of CHEST in macrophages causes these cells to appear foamy and is a characteristic of early stage atherosclerosis (Becker et al. 1994). The SOAT enzymes are being investigated as potential drug targets for atherosclerosis and for Alzheimer's disease (Chang et al. 2009). Alzheimer's disease is a prevalent neurodegenerative disease, characterised by a large extracellular accumulation of amyloid plaques, composed mainly of beta-amyloid peptide aggregates. Increases in free cholesterol in the membrane, which can be caused by inhibiting ACAT1, can lead to the decrease of amyloid precursor protein processing. Pharmacological inhibitors of ACAT1 are potential treatment routes for Alzheimer's disease (Puglielli et al. 2001, Chang et al. 2009, Zhu et al. 2015).

Preceded by: CHOL translocates from lysosome membrane to ER membrane

Followed by: CHEST translocates from ER membrane to lipid particle

Literature references

Chang, TY., Chen, J., Cheng, D., Lin, S., Liu, MS. (1999). Human acyl-CoA:cholesterol acyltransferase-1 in the endoplasmic reticulum contains seven transmembrane domains. *J. Biol. Chem., 274*, 23276-85. ↗

Lackner, KJ., Schmitz, G., Fehringer, P., Böttcher, A., Becker, A., Aslanidis, C. et al. (1994). Purification, cloning, and expression of a human enzyme with acyl coenzyme A: cholesterol acyltransferase activity, which is identical to liver carboxylesterase. *Arterioscler. Thromb., 14*, 1346-55. ↗

Chang, TY., Konopka, G., Tanzi, RE., Berezovska, O., Ingano, LA., Kovacs, DM. et al. (2001). Acyl-coenzyme A: cholesterol acyltransferase modulates the generation of the amyloid beta-peptide. *Nat. Cell Biol., 3*, 905-12. ↗

Guo, D., Song, B., Xiong, Y., Li, Q., Li, B., Zhao, X. et al. (2015). ACAT1 regulates the dynamics of free cholesterols in plasma membrane which leads to the APP-α-processing alteration. *Acta Biochim. Biophys. Sin. (Shanghai), 47*, 951-9. ↗

Li, BL., Urano, Y., Chang, TY., Chang, CC. (2009). Acyl-coenzyme A:cholesterol acyltransferases. *Am. J. Physiol. Endocrinol. Metab., 297*, E1-9. ↗

Editions

2016-06-16	Authored, Edited	Jassal, B.
2016-10-19	Reviewed	D'Eustachio, P.

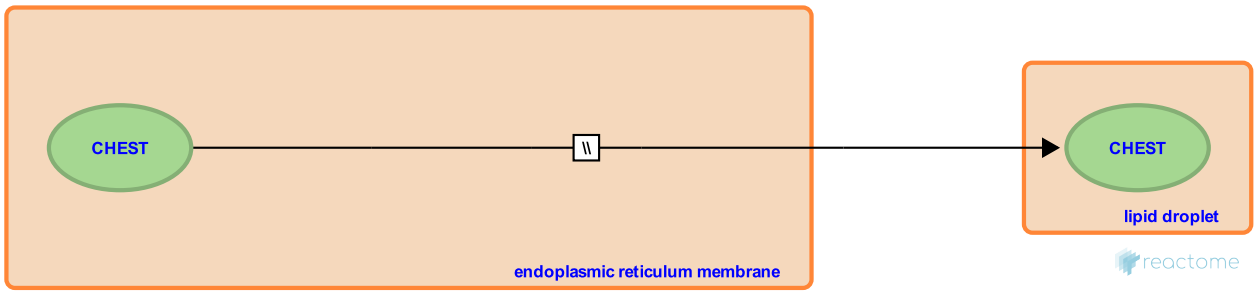
CHEST translocates from ER membrane to lipid particle ↗

Location: LDL clearance

Stable identifier: R-HSA-8876731

Type: omitted

Compartments: endoplasmic reticulum membrane, lipid droplet



Cholesterol that has been esterified by sterol O-acyltransferases at the ER membrane to cholesteryl esters (CHESTs) are stored in lipid particles present in the cytosol (Daugherty et al. 2008).

Preceded by: SOAT1,2 transfer acyl group to CHOL forming CHEST

Literature references

Rateri, DL., Daugherty, A., Lu, H. (2008). As macrophages indulge, atherosclerotic lesions bulge. *Circ. Res., 102*, 1445-7. ↗

Editions

2016-06-16	Authored, Edited	Jassal, B.
2016-10-19	Reviewed	D'Eustachio, P.

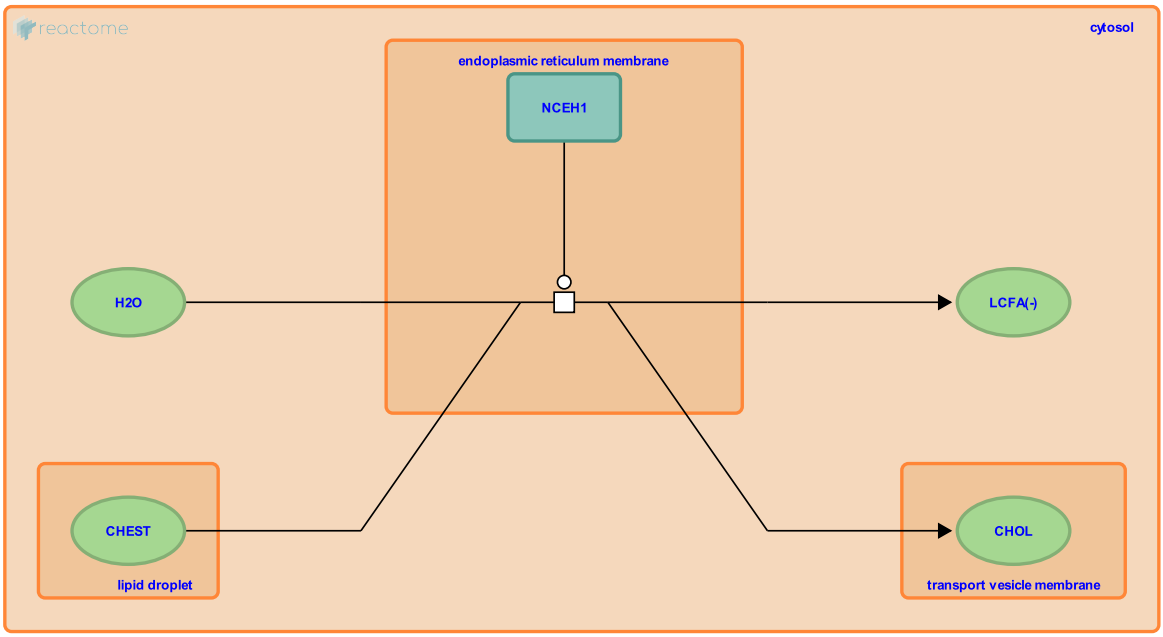
NCEH1 hydrolyzes cholesterol esters ↗

Location: LDL clearance

Stable identifier: R-HSA-6813720

Type: transition

Compartments: endoplasmic reticulum membrane, transport vesicle membrane, lipid droplet, cytosol



NCEH1 (neutral cholesterol ester hydrolase) hydrolyzes cholesterol esters to form cholesterol (CHOL) and free fatty acids (LCFA). In both humans (Igarashi et al. 2010a) and mice (Igarashi et al. 2010b, Okazaki et al. 2008, Sakai et al. 2014) NCEH1 associated with the endoplasmic reticulum membrane appears to play a major role in cholesterol ester hydrolysis in macrophages. Free CHOL is transported via transport vesicles and can be used for cellular functions or removed from the cell by ABCA1 to create new HDL particles.

Literature references

Nakagawa, Y., Amemiya-Kudo, M., Ohta, K., Ohashi, K., Nagai, R., Takase, S. et al. (2008). Identification of neutral cholesterol ester hydrolase, a key enzyme removing cholesterol from macrophages. *J. Biol. Chem., 283*, 33357-64. ↗

Sakai, K., Nagashima, S., Ohshiro, T., Enkhtuvshin, B., Ishibashi, S., Sekiya, M. et al. (2014). Critical role of neutral cholesteryl ester hydrolase 1 in cholesteryl ester hydrolysis in murine macrophages. *J. Lipid Res., 55*, 2033-40. ↗

Ohta, K., Isshiki, M., Kumagai, M., Fujita, T., Nagai, R., Takase, S. et al. (2010). Targeting of neutral cholesterol ester hydrolase to the endoplasmic reticulum via its N-terminal sequence. *J. Lipid Res., 51*, 274-85. ↗

Li, Y., Ohta, K., Ohashi, K., Kumagai, M., Nagai, R., Takase, S. et al. (2010). The critical role of neutral cholesterol ester hydrolase 1 in cholesterol removal from human macrophages. *Circ. Res., 107*, 1387-95. ↗

Editions

2015-11-23	Authored, Edited	D'Eustachio, P.
2015-11-30	Reviewed	Jassal, B.

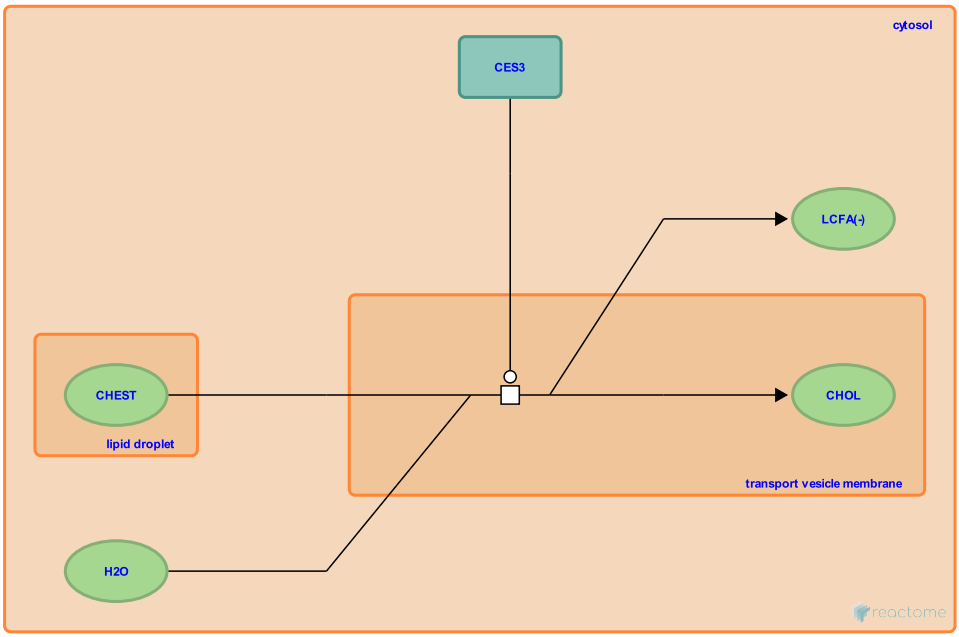
CES3 hydrolyses CHEST to CHOL and LCFA(-) ↗

Location: LDL clearance

Stable identifier: R-HSA-8937442

Type: transition

Compartments: transport vesicle membrane, lipid droplet, cytosol



In macrophage foam cells, the hydrolysis of cholesteryl esters (CHESTs) is the rate-limiting step in the removal of free cholesterol (CHOL) from these cells. CHOL is transported via transport vesicles and can be used for cellular functions or removed from the cell by ABCA1 to create new HDL particles. Accumulation of CHESTs in macrophage foam cells is key to atherosclerotic plaque formation and occurs as a result of an imbalance between CHOL influx and efflux pathways. The main hydrolase that hydrolyses CE in macrophages is neutral cholesterol ester hydrolase 1 (NCEH1). Carboxylesterases (CESs), usually involved in the hydrolysis of drugs, can also hydrolyse CHESTs with CES1 responsible for >70% of the total CES hydrolytic activity in macrophages, thus playing an important antiatherogenic role. CES1 knockdown studies reveal a compensatory increase in the expression of CES3, expressed at <30% of the level of CES1 in human macrophages, which restores intracellular CHEST hydrolytic activity and CHOL efflux (Zhao et al. 2012). Human CES3 isoproteins are predicted to be either secreted or retained in the cytosol (Holmes et al. 2010) but the exact location is currently unknown.

Literature references

Holmes, RS., VandeBerg, JL., Cox, LA. (2010). Mammalian carboxylesterase 3: comparative genomics and proteomics. *Genetica, 138*, 695-708. ↗

Wang, J., Bie, J., Ghosh, S., Zhao, B., Marqueen, SA. (2012). Identification of a novel intracellular cholesteryl ester hydrolase (carboxylesterase 3) in human macrophages: compensatory increase in its expression after carboxylesterase 1 silencing. *Am. J. Physiol., Cell Physiol., 303*, C427-35. ↗

Editions

2016-09-01	Authored, Edited	Jassal, B.
2016-10-17	Reviewed	D'Eustachio, P.

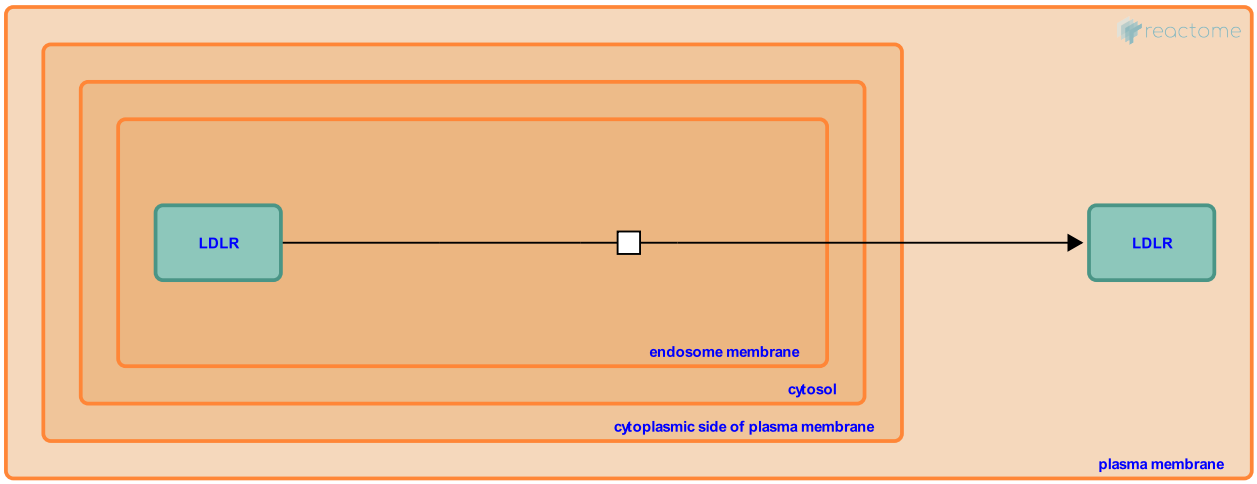
LDLR [endosome membrane] => LDLR [plasma membrane] ↗

Location: LDL clearance

Stable identifier: R-HSA-171087

Type: transition

Compartments: endosome membrane



LDL receptors in the endosome membrane are quickly returned to the cell surface (Goldstein et al. 1979).

Preceded by: LDLR:LDL complex => LDLR + LDL

Followed by: LDL + LDLR => LDL:LDLR complex

Literature references

Goldstein, JL., Brown, MS., Anderson, RG. (1979). Coated pits, coated vesicles, and receptor-mediated endocytosis. *Nature, 279*, 679-85. ↗

Editions

2006-02-20	Edited	D'Eustachio, P.
2007-04-30	Authored	D'Eustachio, P.

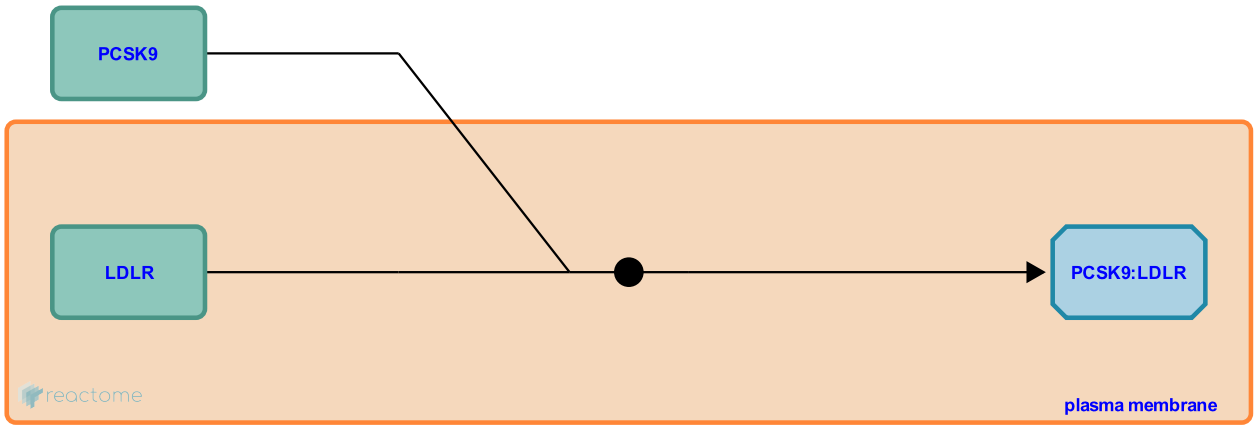
PCSK9 binds LDLR ↗

Location: LDL clearance

Stable identifier: R-HSA-6784734

Type: binding

Compartments: plasma membrane, extracellular region



PCSK9 (Proprotein convertase subtilisin/kexin type 9) binds to LDLR (Low-density lipoprotein receptor) on the cell surface. The binding site of PCSK9 has been localized to the epidermal growth factor-like repeat A (EGF-A) domain of the LDLR (Zhang et al. 2007). The complex PCSK9:LDLR is internalized via clathrin-mediated endocytosis and then routed to lysosomes via a mechanism that does not require ubiquitination and is distinct from the autophagy and proteosomal degradation pathways. In lysosomes, the affinity of the interaction between PCSK9 and LDLR dramatically increases. This promotes the final degradation of PCSK9 and LDLR without recycling. Monoclonal antibodies targeting PCSK9 have been shown to markedly reduce LDL cholesterol levels and are a novel treatment strategy for adults with hypercholesterolemia (Navarese et al. 2015).

Followed by: PCSK9:LDLR bind to Clathrin

Literature references

Kolodziejczak, M., Schulze, V., Brockmeyer, M., Kubica, JM., Gurbel, PA., Lin, Y. et al. (2015). Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. *Ann. Intern. Med., 163*, 40-51. ↗

Garuti, R., Hobbs, HH., Horton, JD., Zhao, Z., Cohen, JC., Zhang, DW. et al. (2007). Binding of proprotein convertase subtilisin/kexin type 9 to epidermal growth factor-like repeat A of low density lipoprotein receptor decreases receptor recycling and increases degradation. *J. Biol. Chem., 282*, 18602-12. ↗

Editions

2015-05-12	Authored	Sanchis, A.
2016-02-11	Edited	Jassal, B.
2016-04-20	Reviewed	D'Eustachio, P.

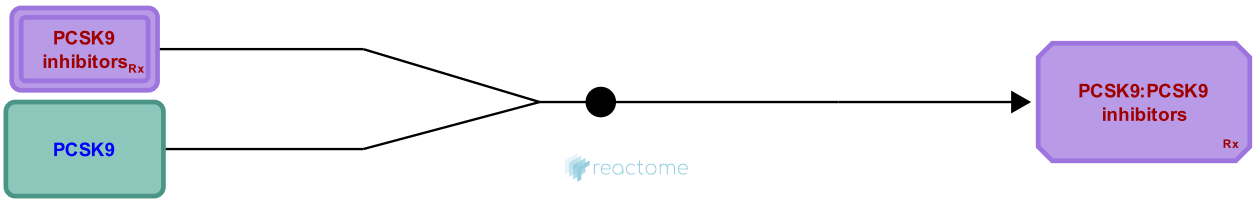
PCSK9 binds PCSK9 inhibitors ↗

Location: LDL clearance

Stable identifier: R-HSA-9733403

Type: binding

Compartments: extracellular region



Low-density lipoprotein (LDL) receptors expressed on hepatocytes mediate the removal of circulating LDL-cholesterol (LDL-C) from plasma via a receptor-mediated endocytic process. High circulating levels of LDL-C contributes to hypercholesterolemia, which is a known risk factor for cardiovascular disease.

The PCSK9 gene produces proprotein convertase subtilisin/kexin type 9 (neural apoptosis-regulated convertase 1, NARC1), an important regulator of plasma cholesterol homeostasis (Seidah et al. 2003). It binds to low-density lipoprotein receptor (LDLR) family members and promotes their degradation in intracellular acidic compartments (Poirer et al. 2008). This results in lower numbers of LDLRs on the surface of hepatocytes and as a consequence, circulating plasma levels of LDL-C are elevated.

The monoclonal antibodies alirocumab and evolocumab are approved PCSK9 inhibitor drugs for the treatment of familial hypercholesterolemia and dyslipidemias (Devito et al. 2015, Page & Watts 2015) . These antibodies bind PCSK9 on its catalytic site resulting in steric inhibition of binding between PCSK9 and LDL receptors (Duff et al. 2009).

Literature references

Fok, M., Lam, CWK., Tomlinson, B., Patil, NG. (2021). Role of PCSK9 Inhibitors in Patients with Familial Hypercholesterolemia. *Endocrinol Metab (Seoul), 36*, 279-295. ↗

Kirby, IT., Duff, CJ., Hooper, NM., Hutchinson, SE., Scott, MJ., Martin, SL. (2009). Antibody-mediated disruption of the interaction between PCSK9 and the low-density lipoprotein receptor. *Biochem J, 419*, 577-84. ↗

Editions

2021-06-04	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

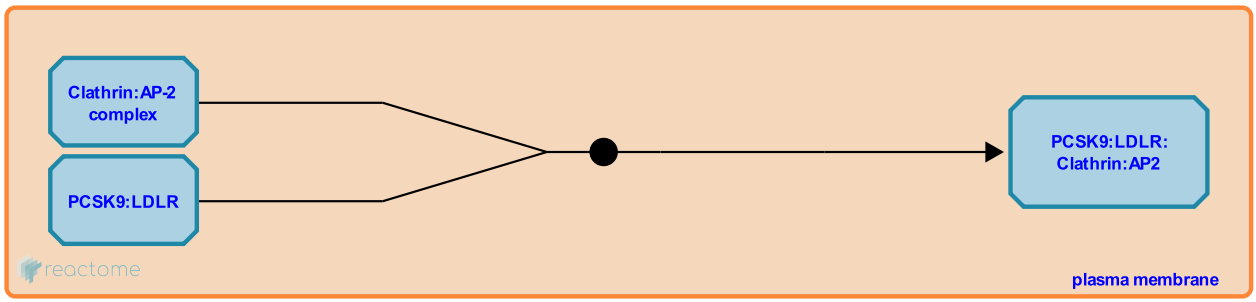
PCSK9:LDLR bind to Clathrin ↗

Location: LDL clearance

Stable identifier: R-HSA-6784735

Type: binding

Compartments: plasma membrane, clathrin-coated endocytic vesicle membrane



LDLR that engage PCSK9 at the cell membrane are internalized via the canonical clathrin-dependent endocytic machinery (Wang et al. 2012). This complex is routed to lysosomes via a pathway that does not require ubiquitination of the cytoplasmic tail of the receptor and does not involve the proteasomal or autophagy pathways. The clathrin is required for the internalization of the LDLR-PCSK9 complex that forms on the cell surface.

Preceded by: PCSK9 binds LDLR

Followed by: PCSK9:LDLR:Clathrin-coated vesicle transport from plasma membrane to endolysosome

Literature references

Huang, Y., Hobbs, HH., Cohen, JC., Wang, Y. (2012). Molecular characterization of proprotein convertase subtilisin/kexin type 9-mediated degradation of the LDLR. *J. Lipid Res., 53*, 1932-43. ↗

Editions

2015-05-12	Authored	Sanchis, A.
2016-02-11	Edited	Jassal, B.
2016-04-20	Reviewed	D'Eustachio, P.

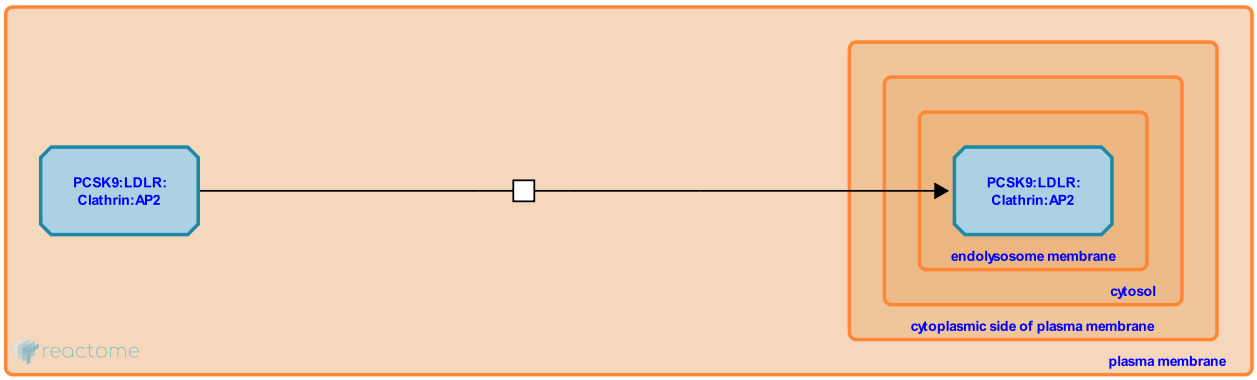
PCSK9:LDLR:Clathrin-coated vesicle transport from plasma membrane to endolysosome ↗

Location: LDL clearance

Stable identifier: R-HSA-6784729

Type: transition

Compartments: plasma membrane, endolysosome membrane



The PCSK9:LDLR:Clathrin-coated vesicle is internalized to endosomes and, after that, to lysosomes where PCSK9 and LDLR are degraded (Wang et al. 2012).

Preceded by: PCSK9:LDLR bind to Clathrin

Followed by: Degradation of PCSK9:LDLR:Clathrin-coated vesicle

Literature references

Huang, Y., Hobbs, HH., Cohen, JC., Wang, Y. (2012). Molecular characterization of proprotein convertase subtilisin/kexin type 9-mediated degradation of the LDLR. *J. Lipid Res., 53*, 1932-43. ↗

Editions

2015-05-12	Authored	Sanchis, A.
2016-02-11	Edited	Jassal, B.
2016-04-20	Reviewed	D'Eustachio, P.

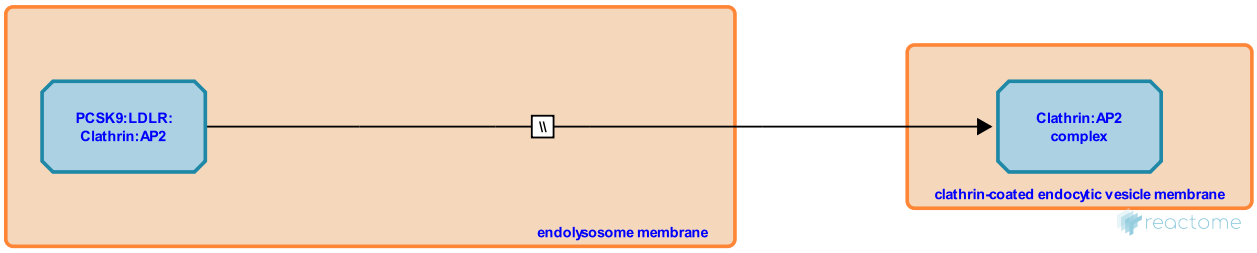
Degradation of PCSK9:LDLR:Clathrin-coated vesicle ↗

Location: LDL clearance

Stable identifier: R-HSA-6784738

Type: omitted

Compartments: endolysosome membrane, clathrin-coated endocytic vesicle membrane



LDLR that engage PCSK9 at the cell membrane are internalized via the canonical clathrin-dependent endocytic machinery (Wang et al. 2012). This complex is routed to lysosomes via a pathway that does not require ubiquitination of the cytoplasmic tail of the receptor and does not involve the proteasomal or autophagy pathways. The clathrin is required for the internalization of the LDLR-PCSK9 complex that forms on the cell surface.

Preceded by: PCSK9:LDLR:Clathrin-coated vesicle transport from plasma membrane to endolysosome

Literature references

Huang, Y., Hobbs, HH., Cohen, JC., Wang, Y. (2012). Molecular characterization of proprotein convertase subtilisin/kexin type 9-mediated degradation of the LDLR. *J. Lipid Res., 53*, 1932-43. ↗

Editions

2015-05-12	Authored	Sanchis, A.
2016-02-11	Edited	Jassal, B.
2016-04-20	Reviewed	D'Eustachio, P.

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