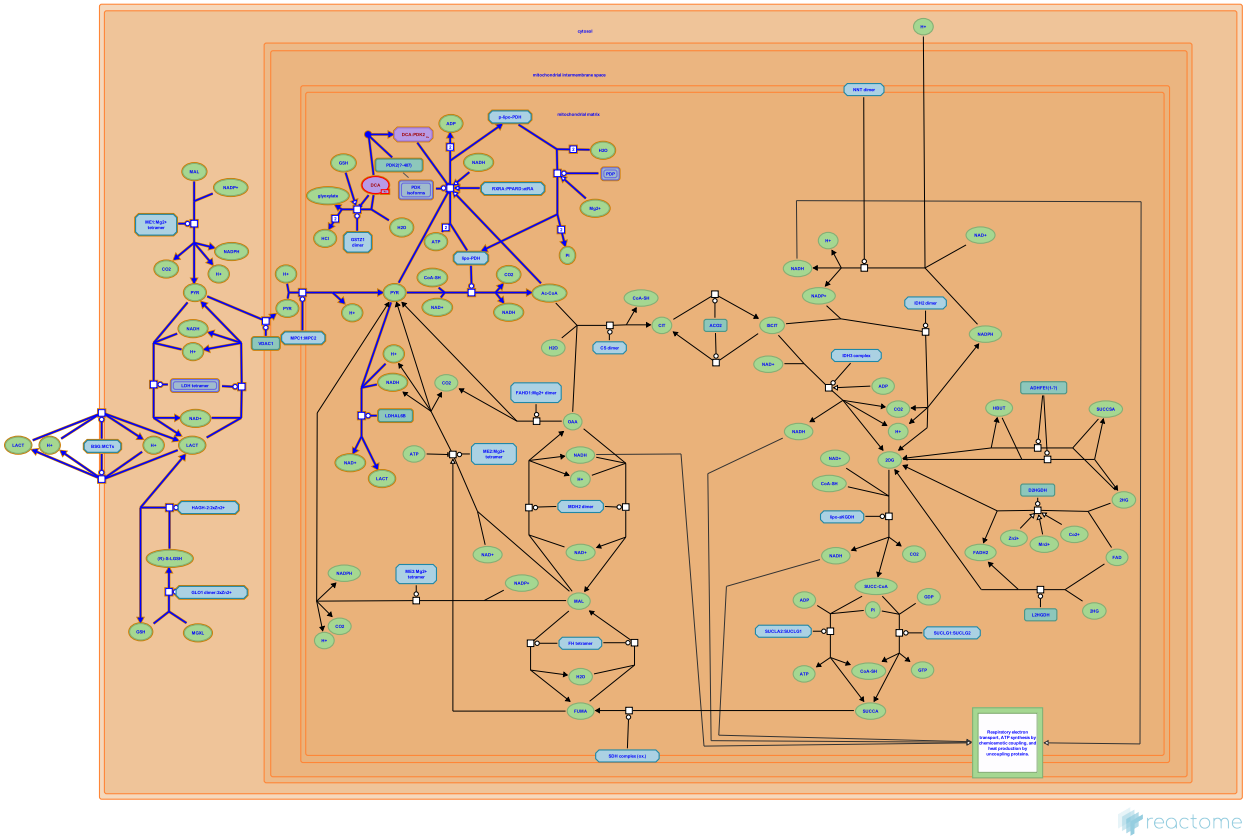
Pyruvate metabolism



Birney, E., D'Eustachio, P., Gopinathrao, G., Harris, RA., Hung, HC., Jassal, B., Rutter, J., Schmidt, EE.

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

27/02/2021

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. ↗

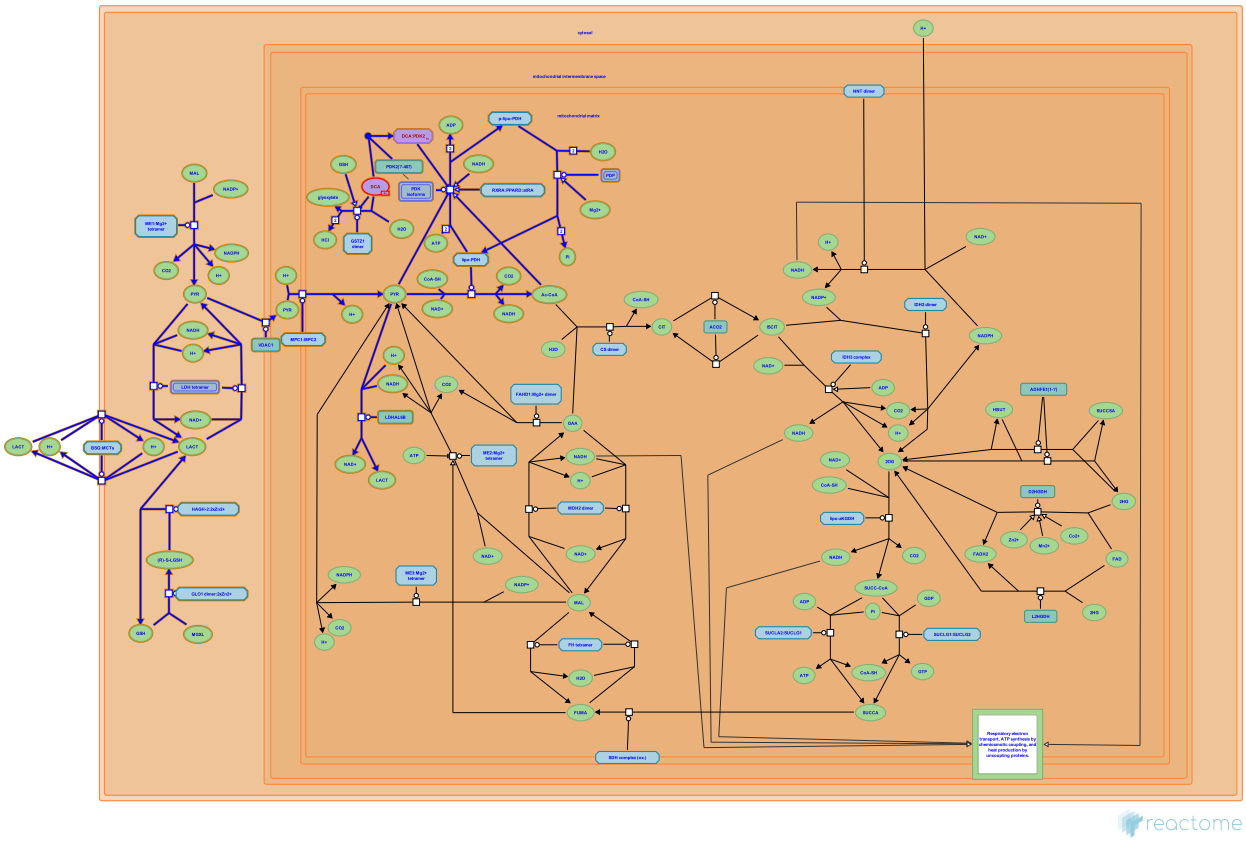
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Pyruvate metabolism ↗

Stable identifier: R-HSA-70268



Pyruvate sits at an intersection of key pathways of energy metabolism. It is the end product of glycolysis and the starting point for gluconeogenesis, and can be generated by transamination of alanine. It can be converted by the pyruvate dehydrogenase complex to acetyl CoA (Reed and Hackert 1990) which can enter the TCA cycle or serve as the starting point for the syntheses of long chain fatty acids, steroids, and ketone bodies depending on the tissue and metabolic state in which it is formed. It also plays a central role in balancing the energy needs of various tissues in the body. Under conditions in which oxygen supply is limiting, e.g., in exercising muscle, or in the absence of mitochondria, e.g., in red blood cells, re-oxidation of NADH produced by glycolysis cannot be coupled to generation of ATP. Instead, re-oxidation is coupled to the reduction of pyruvate to lactate. This lactate is released into the blood, and is taken up primarily by the liver, where it is oxidized to pyruvate and can be used for gluconeogenesis (Cori 1981).

Literature references

Reed, LJ., Hackert, ML. (1990). Structure-function relationships in dihydrolipoamide acyltransferases. *J Biol Chem, 265*, 8971-4. ↗

Cori, CF. (1981). The glucose-lactic acid cycle and gluconeogenesis. *Curr Top Cell Regul, 18*, 377-87. ↗

Editions

2009-12-18	Revised	D'Eustachio, P.

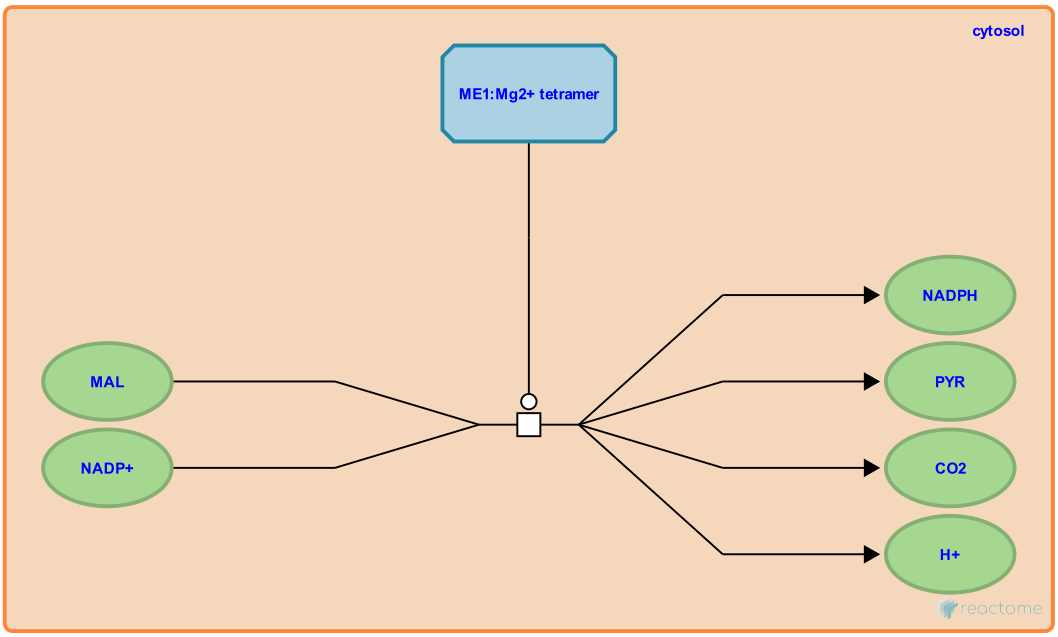
ME1:Mg2+ tetramer oxidatively decarboxylates MAL to PYR ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-9012036

Type: transition

Compartments: cytosol



One hallmark of cancer is altered cellular metabolism. Malic enzymes (MEs) are a family of homotetrameric enzymes that catalyse the reversible oxidative decarboxylation of L-malate to pyruvate, with a simultaneous reduction of NAD(P)+ to NAD(P)H. As MEs generate NADPH and NADH, they may play roles in energy production and reductive biosynthesis. Humans possess three ME isoforms; ME1 is cytosolic and utilises NADP+, ME3 is mitochondrial and can utilise NADP+ and ME2 is mitochondrial and can utililse either NAD+ or NADP+ (Chang & Tong 2003, Murugan & Hung 2012).

NADP-dependent malic enzyme (ME1, aka c-NADP-ME) is a cytosolic enzyme that oxidatively decarboxylates (s)-malate (MAL) to pyruvate (PYR) and CO2 using NADP+ as cofactor (Zelewski & Swierczynski 1991). ME1 exists as a dimer of dimers (Murugan & Hung 2012, Hsieh et al. 2014) and a divalent metal such as Mg2+ is essential for catalysis (Chang & Tong 2003).

Followed by: VDAC1 transports PYR from cytosol to mitochondrial intermembrane space, LDH tetramer reduces PYR to LACT

Literature references

Zelewski, M., Swierczyński, J. (1991). Malic enzyme in human liver. Intracellular distribution, purification and properties of cytosolic isozyme. *Eur. J. Biochem., 201*, 339-45. ↗

Chang, GG., Tong, L. (2003). Structure and function of malic enzymes, a new class of oxidative decarboxylases. *Biochemistry, 42*, 12721-33. ↗

Hsieh, JY., Li, SY., Chen, MC., Yang, PC., Chen, HY., Chan, NL. et al. (2014). Structural characteristics of the nonallosteric human cytosolic malic enzyme. *Biochim. Biophys. Acta, 1844*, 1773-83. ↗

Murugan, S., Hung, HC. (2012). Biophysical characterization of the dimer and tetramer interface interactions of the human cytosolic malic enzyme. *PLoS ONE, 7*, e50143. ↗

Editions

2017-07-10	Authored, Edited	Jassal, B.
2018-01-30	Reviewed	Hung, HC.

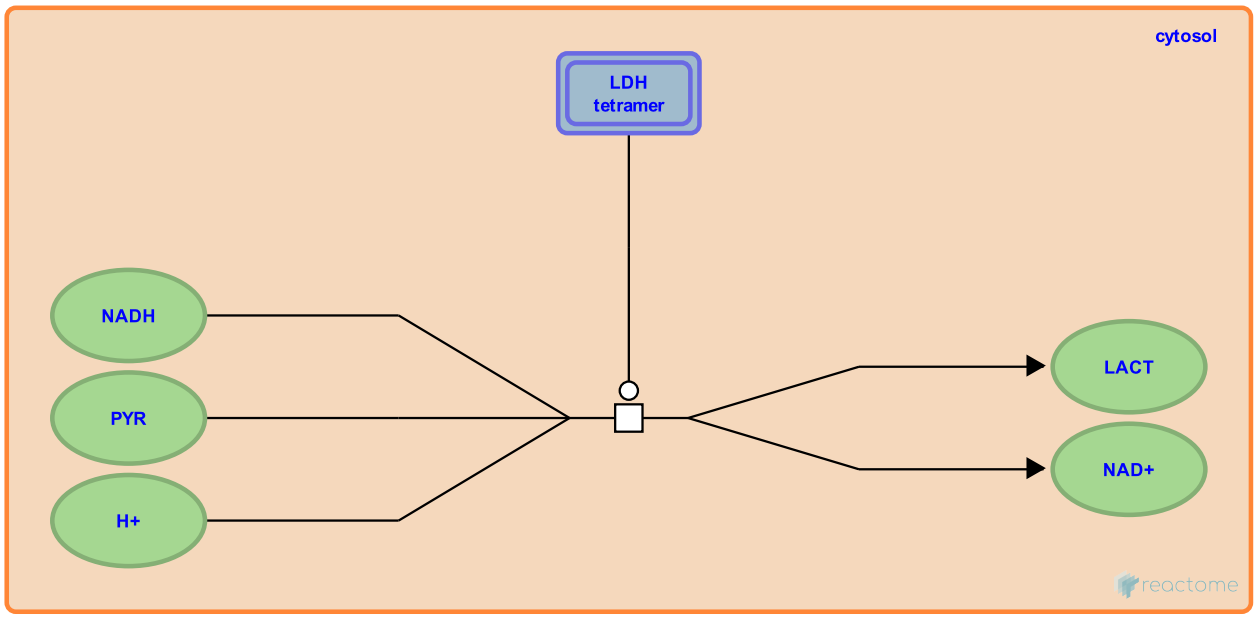
LDH tetramer reduces PYR to LACT ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-71849

Type: transition

Compartments: cytosol



Cytosolic lactate dehydrogenase (LDH) catalyzes the freely reversible reaction of pyruvate (PYR) and NADH + H+ to form lactate (LACT) and NAD+. In liver parenchymal cells, this reaction allows lactate from red blood cells and exercising muscle to be converted to pyruvate which in turn is typically used for gluconeogenesis which also consumes the NADH from the reaction.

Lactate dehydrogenase is active as a tetramer. Two isoforms of lactate dehydrogenase, A and B, are widely expressed in human tissues, and all five tetramers - A4, A3B, A2B2, AB3, and B4 - are found (Read et al. 2001; Sakai et al. 1987; Yu et al. 2001). A third isoform, C, and its tetramer, C4, are found in testis (Millan et al. 1987; LeVan & Goldberg 1991). A fourth isoform, LDHAL6A, is less fully characterized than these others but limited data suggest that it may be testis-specific (Chen et al. 2009).

Preceded by: ME1:Mg2+ tetramer oxidatively decarboxylates MAL to PYR

Literature references

Chen, X., Gu, X., Shan, Y., Tang, W., Yuan, J., Zhong, Z. et al. (2009). Identification of a novel human lactate dehydrogenase gene LDHAL6A, which activates transcriptional activities of AP1(PMA). *Mol. Biol. Rep., 36*, 669-76. ↗

LeVan, KM., Goldberg, E. (1991). Properties of human testis-specific lactate dehydrogenase expressed from Escherichia coli. *Biochem. J., 273*, 587-92. ↗

Millan, JL., Driscoll, CE., LeVan, KM., Goldberg, E. (1987). Epitopes of human testis-specific lactate dehydrogenase deduced from a cDNA sequence. *Proc. Natl. Acad. Sci. U.S.A., 84*, 5311-5. ↗

Read, JA., Winter, VJ., Eszes, CM., Sessions, RB., Brady, RL. (2001). Structural basis for altered activity of M- and H-isozyme forms of human lactate dehydrogenase. *Proteins, 43*, 175-85. ↗

Sakai, I., Sharief, FS., Pan, YC., Li, SS. (1987). The cDNA and protein sequences of human lactate dehydrogenase B. *Biochem J, 248*, 933-6. ↗

Editions

2009-12-18	Revised	D'Eustachio, P.

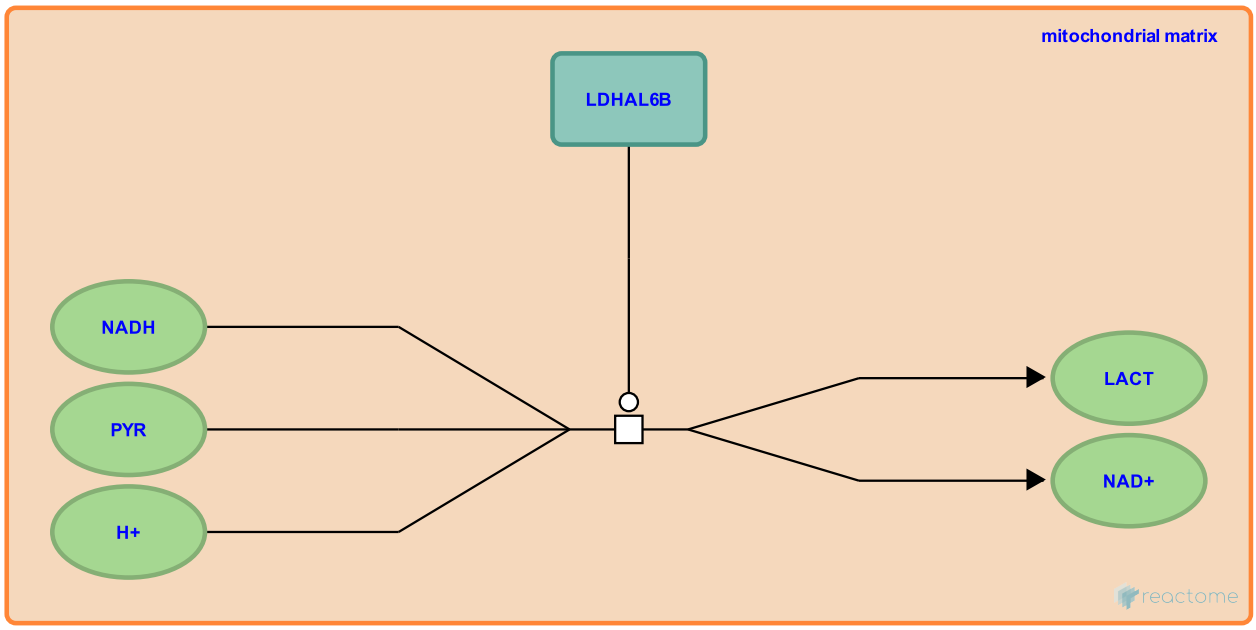
LDHAL6B reduces PYR to LACT ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-6807826

Type: transition

Compartments: mitochondrial matrix



LDHAL6B (L-lactate dehydrogenase A-like 6B) catalyzes the reaction of PYR (pyruvate) and NADH + H+ to form LACT (lactate) and NAD+. The LDHAL6B protein is the inferred product of an open reading frame transcribed in the testis (Wang et al. 2005). Its mitochondrial localization is inferred from the presence of a mitochondrial localization sequence at its amino terminus (Holmes and Goldberg 2009). A physiological role for lactate formation from the abundant pyruvate and NADH expected in rapidly respiring mitochondria is not straightforward to imagine, however.

Literature references

Holmes, RS., Goldberg, E. (2009). Computational analyses of mammalian lactate dehydrogenases: human, mouse, opossum and platypus LDHs. *Comput Biol Chem, 33*, 379-85. ↗

Wang, H., Zhou, Z., Lu, L., Xu, Z., Sha, J. (2005). Cloning and characterization of a novel intronless lactate dehydrogenase gene in human testis. *Int. J. Mol. Med., 15*, 949-53. ↗

Editions

2015-11-09	Authored, Edited, Revised	D'Eustachio, P.
2015-11-09	Reviewed	Jassal, B.

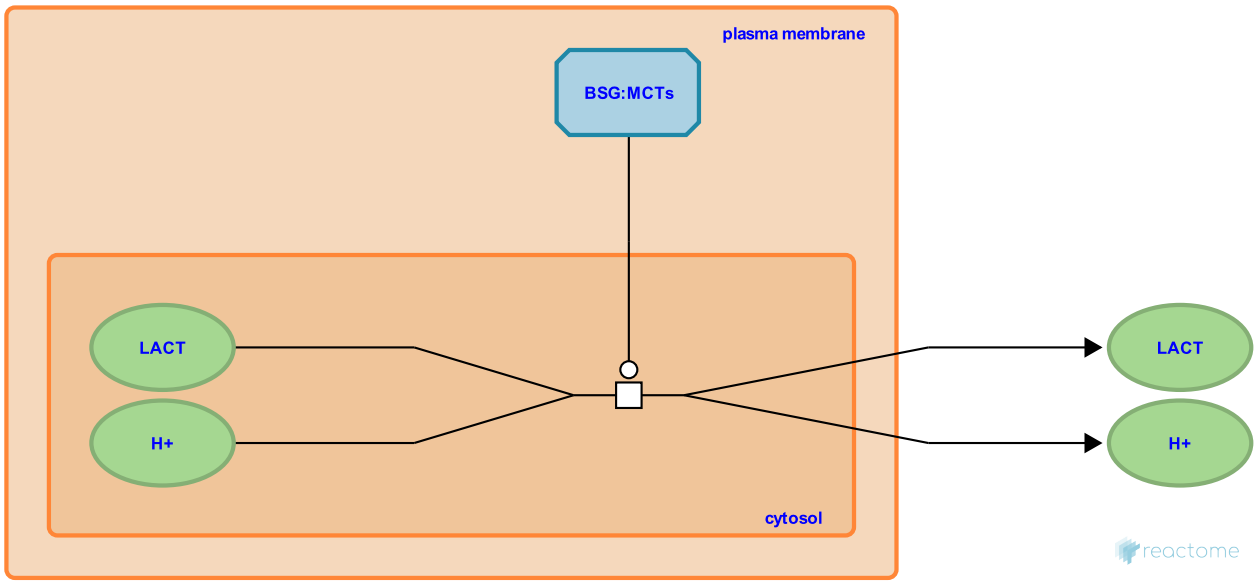
BSG:MCTs cotransport LACT, H+ from cytosol to extracellular region ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-373875

Type: transition

Compartments: cytosol, plasma membrane, extracellular region



The membrane-associated MCT:basigin complex mediates the reversible export of cytosolic lactate and H+ (Wilson et al. 2005).

Literature references

Wilson, MC., Meredith, D., Fox, JE., Manoharan, C., Davies, AJ., Halestrap, AP. (2005). Basigin (CD147) is the target for organomercurial inhibition of monocarboxylate transporter isoforms 1 and 4: the ancillary protein for the insensitive MCT2 is EMBIGIN (gp70). *J Biol Chem, 280,* 27213-21. ↗

Editions

2008-07-17	Authored, Edited	D'Eustachio, P.
2009-12-18	Revised	D'Eustachio, P.

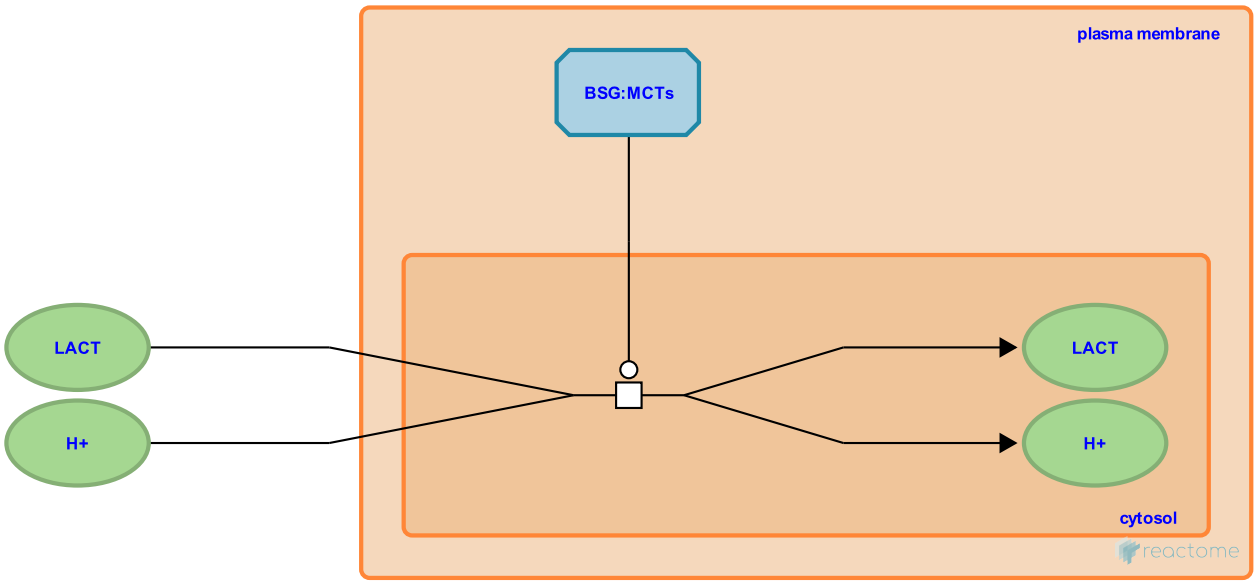
BSG:MCTs cotransport LACT, H+ from extracellular region to cytosol ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-373867

Type: transition

Compartments: cytosol, plasma membrane, extracellular region



The membrane-associated MCT:basigin complex mediates the reversible uptake of extracellular lactate and H+ (Wilson et al. 2005).

Literature references

Wilson, MC., Meredith, D., Fox, JE., Manoharan, C., Davies, AJ., Halestrap, AP. (2005). Basigin (CD147) is the target for organomercurial inhibition of monocarboxylate transporter isoforms 1 and 4: the ancillary protein for the insensitive MCT2 is EMBIGIN (gp70). *J Biol Chem, 280,* 27213-21. ↗

Editions

2008-07-17	Authored, Edited	D'Eustachio, P.
2009-12-18	Revised	D'Eustachio, P.

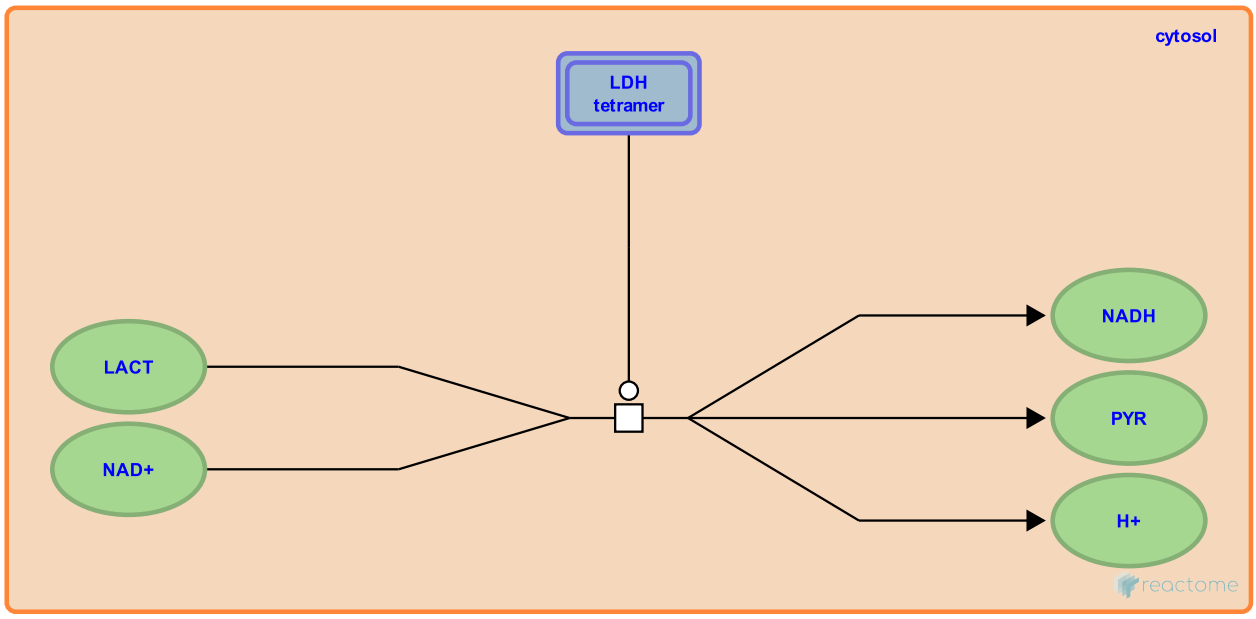
LDH tetramer oxidises LACT to PYR ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-70510

Type: transition

Compartments: cytosol



Cytosolic lactate dehydrogenase catalyzes the freely reversible reaction of lactate and NAD+ to form pyruvate and NADH + H+. In liver parenchymal cells, this reaction allows lactate from red blood cells and exercising muscle to be converted to pyruvate which in turn is typically used for gluconeogenesis which also consumes the NADH from the reaction.

Lactate dehydrogenase is active as a tetramer. Two isoforms of lactate dehydrogenase, A and B, are widely expressed in human tissues, and all five tetramers - A4, A3B, A2B2, AB3, and B4 - are found (Read et al. 2001; Sakai et al. 1987; Yu et al. 2001). A third isoform, C, and its tetramer, C4, are found in testis (Millan et al. 1987; LeVan & Goldberg 1991). A fourth isoform, LDHAL6A, is less fully characterized than these others but limited data suggest that it may be testis-specific (Chen et al. 2009).

Followed by: VDAC1 transports PYR from cytosol to mitochondrial intermembrane space, MPC1:MPC2 cotransports PYR, H+ from cytosol to mitochondrial matrix

Literature references

Chen, X., Gu, X., Shan, Y., Tang, W., Yuan, J., Zhong, Z. et al. (2009). Identification of a novel human lactate dehydrogenase gene LDHAL6A, which activates transcriptional activities of AP1(PMA). *Mol. Biol. Rep., 36*, 669-76. ↗

LeVan, KM., Goldberg, E. (1991). Properties of human testis-specific lactate dehydrogenase expressed from Escherichia coli. *Biochem. J., 273*, 587-92. ↗

Millan, JL., Driscoll, CE., LeVan, KM., Goldberg, E. (1987). Epitopes of human testis-specific lactate dehydrogenase deduced from a cDNA sequence. *Proc. Natl. Acad. Sci. U.S.A., 84*, 5311-5. ↗

Read, JA., Winter, VJ., Eszes, CM., Sessions, RB., Brady, RL. (2001). Structural basis for altered activity of M- and H-isozyme forms of human lactate dehydrogenase. *Proteins, 43*, 175-85. ↗

Sakai, I., Sharief, FS., Pan, YC., Li, SS. (1987). The cDNA and protein sequences of human lactate dehydrogenase B. *Biochem J, 248*, 933-6. ↗

Editions

2009-12-18	Revised	D'Eustachio, P.
2015-11-09	Revised	D'Eustachio, P.
2015-11-09	Reviewed	Jassal, B.

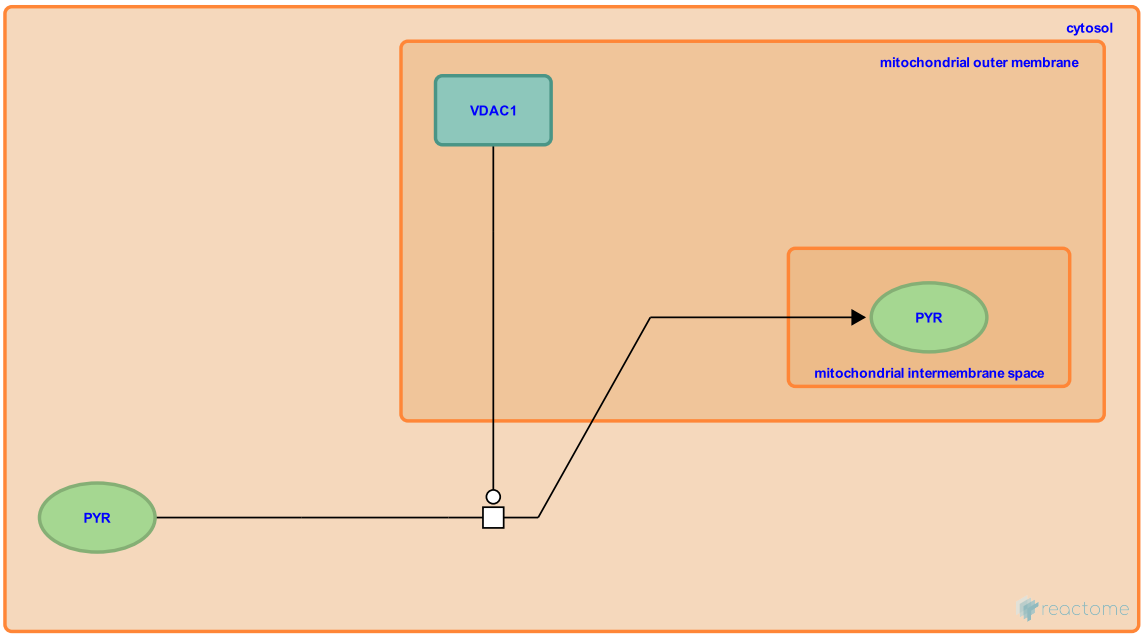
VDAC1 transports PYR from cytosol to mitochondrial intermembrane space ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-9012374

Type: transition

Compartments: cytosol, mitochondrial intermembrane space, mitochondrial outer membrane



Similar to other ions and metabolites, pyruvate (PYR) probably crosses the outer mitochondrial membrane through the relatively non-specific, voltage-dependent anion-selective channel protein 1 (VDAC1) (McCommis & Finck 2015). Humans with defective VDAC1 show impaired PYR oxidation and ATP production (Huizing et al. 1996).

Preceded by: LDH tetramer oxidises LACT to PYR, ME1:Mg2+ tetramer oxidatively decarboxylates MAL to PYR

Literature references

Huizing, M., Ruitenbeek, W., Thinnes, FP., DePinto, V., Wendel, U., Trijbels, FJ. et al. (1996). Deficiency of the voltage-dependent anion channel: a novel cause of mitochondriopathy. *Pediatr. Res., 39*, 760-5. ↗

Editions

2017-07-13	Authored, Edited	Jassal, B.
2018-04-03	Reviewed	Rutter, J.

MPC1:MPC2 cotransports PYR, H+ from cytosol to mitochondrial matrix ↗

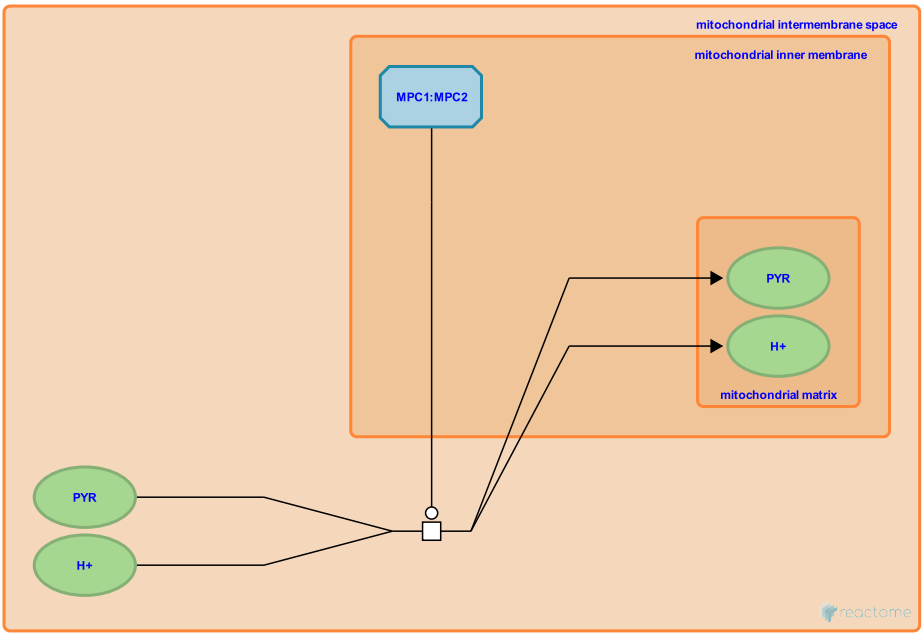
Location: Pyruvate metabolism

Stable identifier: R-HSA-372342

Type: transition

Compartments: mitochondrial intermembrane space, mitochondrial inner membrane, mitochondrial matrix

Inferred from: Cytosolic PYR is transported to the mitochondrial matrix (Rattus norvegicus)



Pyruvate (PYR) and a proton (H+) are cotransported from the mitochondrial intermembrane space to the mitochondrial matrix, mediated by a complex of mitochondrial pyruvate carriers 1 and 2 (MCP1 and MCP2) located in the inner mitochondrial membrane (McCommis & Finck 2015). The proton gradient across the inner mitochondrial membrane must be maintained for ATP production to occur. Transport of PYR across this membrane would collapse this gradient therefore PYR is cotransported with H+. Studies of pyruvate uptake in rat indicate that it is specific, saturable, and competitively inhibitable, indicating a specific role for a membrane transport protein (Papa et al. 1971, Halestrap & Denton 1974), and the stoichiometry of the human reaction is inferred from this work. MCP1 and MCP2 have been identified as essential components of the transporter based on the observation that expression of both proteins (but not either one alone) restored mitochondrial pyruvate uptake in mutant budding yeast. The proteins form a multimeric complex; its stoichiometry is unknown (Bricker et al. 2012).

Preceded by: LDH tetramer oxidises LACT to PYR

Followed by: lipo-PDH decarboxylates PYR to Ac-CoA

Literature references

Bricker, DK., Taylor, EB., Schell, JC., Orsak, T., Boutron, A., Chen, YC. et al. (2012). A mitochondrial pyruvate carrier required for pyruvate uptake in yeast, Drosophila, and humans. *Science, 337*, 96-100. ↗

Halestrap, AP., Denton, RM. (1974). Specific inhibition of pyruvate transport in rat liver mitochondria and human erythrocytes by alpha-cyano-4-hydroxycinnamate. *Biochem. J., 138*, 313-6. ↗

Papa, S., Francavilla, A., Paradies, G., Meduri, B. (1971). The transport of pyruvate in rat liver mitochondria. *FEBS Lett, 12*, 285-288. ↗

Editions

2008-06-20	Authored	D'Eustachio, P.
2008-09-10	Reviewed	Harris, RA.
2008-09-13	Edited	D'Eustachio, P.
2009-12-18	Revised	D'Eustachio, P.
2012-10-12	Revised	D'Eustachio, P.
2012-10-12	Reviewed	Jassal, B.

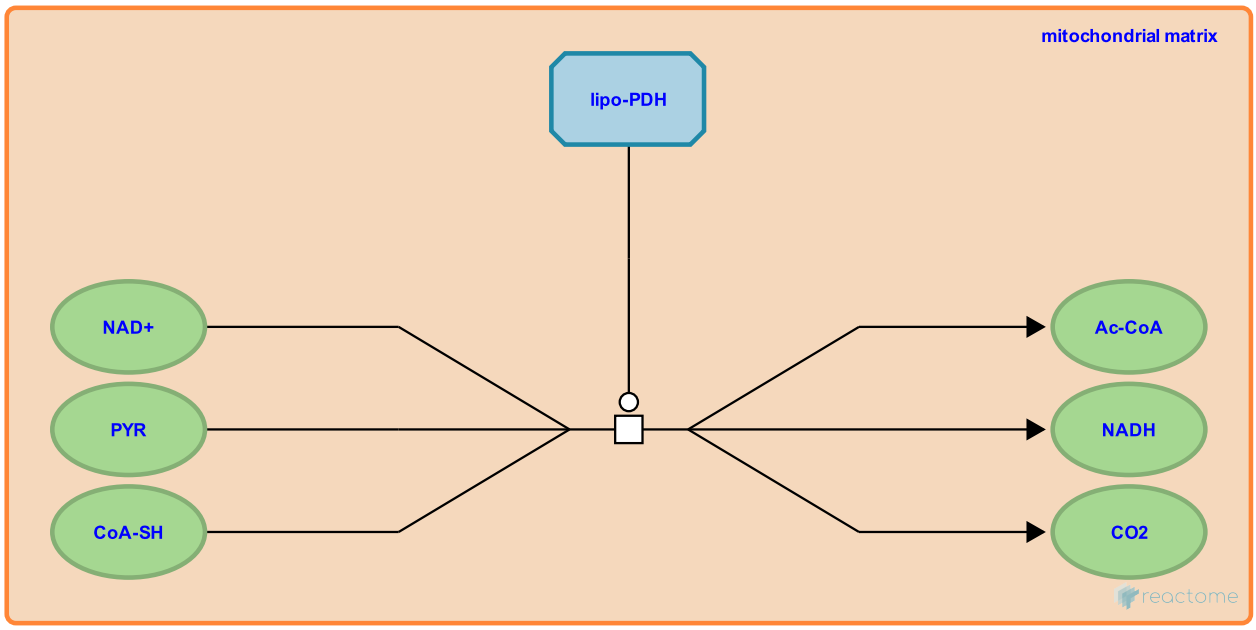
lipo-PDH decarboxylates PYR to Ac-CoA ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-71397

Type: transition

Compartments: mitochondrial matrix



The mitochondrial pyruvate dehydrogenase complex catalyzes the reaction of pyruvate, CoASH, and NAD+ to form acetylCoA, CO2, and NADH. The enzyme complex contains multiple copies of three different proteins, E1 alpha, E1 beta, E2, and E3, each with distinct catalytic activities (Reed and Hackert 1990; Zhou et al 2001). The reaction starts with the oxidative decarboxylation of pyruvate catalyzed by E1 alpha and beta (pyruvate dehydrogenase). Lipoamide cofactor associated with E1 is reduced at the same time. Next, the acetyl group derived from pyruvate is transferred to coenzyme A in two steps catalyzed by E2 (dihydrolipolyl transacetylase). Finally, the oxidized form of lipoamide is regenerated and electrons are transferred to NAD+ in two steps catalyzed by E3 (dihydrolipoyl dehydrogenase). The biochemical details of this reaction have been worked out with pyruvate dehydrogenase complex and subunits purified from bovine tissue and other non-human sources. Direct evidence for the roles of the corresponding human proteins comes from studies of patients expressing mutant forms of E1 alpha (Lissens et al. 2000), E1 beta (Brown et al. 2004), E2 (Head et al. 2005), and E3 (Brautigam et al. 2005).

Preceded by: MPC1:MPC2 cotransports PYR, H+ from cytosol to mitochondrial matrix

Literature references

Brautigam, CA., Chuang, JL., Tomchick, DR., Machius, M., Chuang, DT. (2005). Crystal structure of human dihydrolipoamide dehydrogenase: NAD+/NADH binding and the structural basis of disease-causing mutations. *J Mol Biol, 350*, 543-52. ↗

Brown, RM., Head, RA., Boubriak, II., Leonard, JV., Thomas, NH., Brown, GK. (2004). Mutations in the gene for the E1beta subunit: a novel cause of pyruvate dehydrogenase deficiency. *Hum Genet, 115*, 123-7. ↗

Head, RA., Brown, RM., Zolkipli, Z., Shahdadpuri, R., King, MD., Clayton, PT. et al. (2005). Clinical and genetic spectrum of pyruvate dehydrogenase deficiency: dihydrolipoamide acetyltransferase (E2) deficiency. *Ann Neurol, 58*, 234-41. ↗

Lissens, W., De Meirleir, L., Seneca, S., Liebaers, I., Brown, GK., Brown, RM. et al. (2000). Mutations in the X-linked pyruvate dehydrogenase (E1) alpha subunit gene (PDHA1) in patients with a pyruvate dehydrogenase complex deficiency. *Hum Mutat, 15*, 209-19. ↗

Reed, LJ., Hackert, ML. (1990). Structure-function relationships in dihydrolipoamide acyltransferases. *J Biol Chem, 265*, 8971-4. ↗

Editions

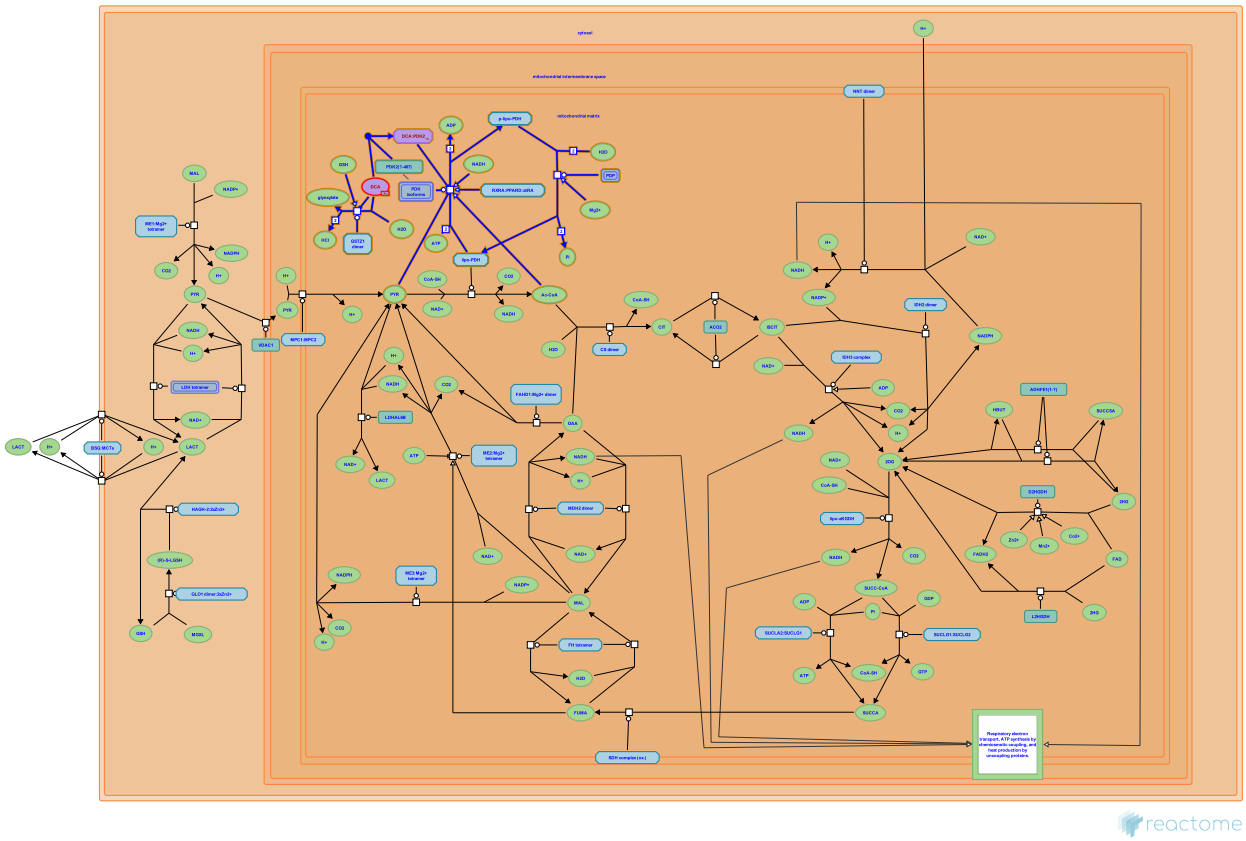
2003-01-28	Authored	Schmidt, EE., Birney, E.
2009-12-18	Revised	D'Eustachio, P.
2020-11-17	Edited	D'Eustachio, P.

Regulation of pyruvate dehydrogenase (PDH) complex ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-204174

Compartments: mitochondrial matrix



The mitochondrial pyruvate dehydrogenase (PDH) complex catalyzes the oxidative decarboxylation of pyruvate, linking glycolysis to the tricarboxylic acid cycle and fatty acid synthesis. PDH inactivation is crucial for glucose conservation when glucose is scarce, while adequate PDH activity is required to allow both ATP and fatty acid production from glucose. The mechanisms that control human PDH activity include its phosphorylation (inactivation) by pyruvate dehydrogenase kinases (PDK 1-4) and its dephosphorylation (activation, reactivation) by pyruvate dehydrogenase phosphate phosphatases (PDP 1 and 2). Isoform-specific differences in kinetic parameters, regulation, and phosphorylation site specificity of the PDKs introduce variations in the regulation of PDC activity in differing endocrine and metabolic states (Sugden and Holness 2003).

Literature references

Sugden, MC., Holness, MJ. (2003). Recent advances in mechanisms regulating glucose oxidation at the level of the pyruvate dehydrogenase complex by PDKs. *Am J Physiol Endocrinol Metab, 284*, E855-62. ↗

Editions

2007-11-27	Authored	Gopinathrao, G.
2008-01-12	Reviewed	D'Eustachio, P.
2009-12-18	Revised	D'Eustachio, P.

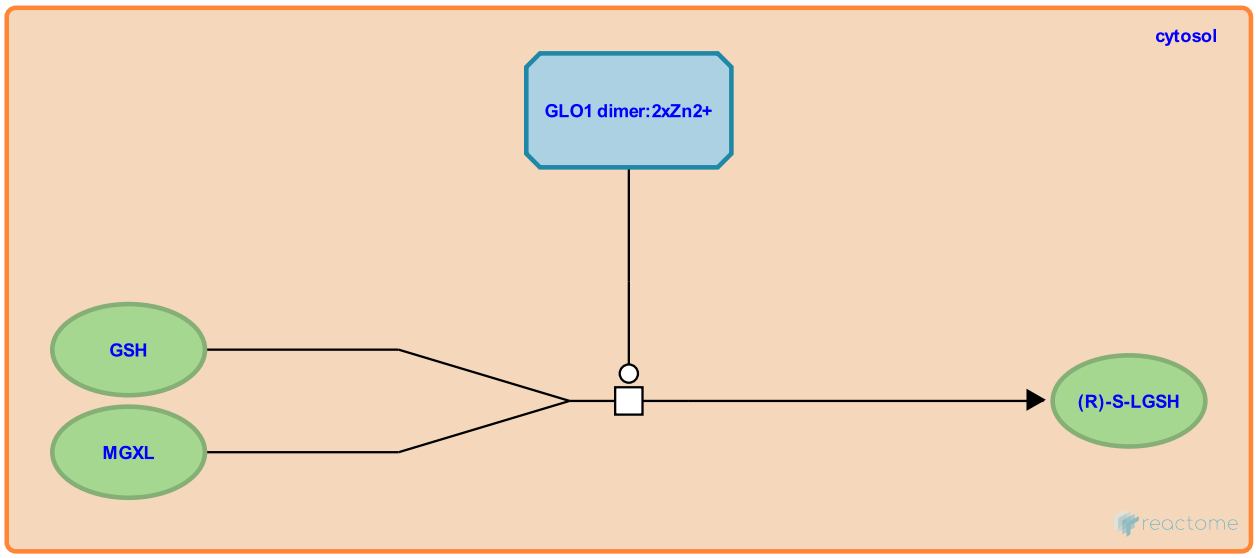
GLO1 dimer:2xZn2+ transforms MGXL and GSH to (R)-S-LGSH ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-5694071

Type: transition

Compartments: cytosol



Lactoylglutathione lyase (GLO1) catalyses the transformation of methylglyoxal (MGXL) and glutathione (GSH) to (R)-S-lactoylglutathione ((R)-S-LGSH), an intermediate in pyruvate metabolism. MGXL is a reactive 2-oxoaldehyde byproduct of normal metabolism that is a carcinogen and a mutagen (Ridderstrom et al. 1998). This is the first step in the glyoxalase system, a critical two-step detoxification system for MGXL.

Literature references

Ridderström, M., Cameron, AD., Jones, TA., Mannervik, B. (1998). Involvement of an active-site Zn2+ ligand in the catalytic mechanism of human glyoxalase I. *J. Biol. Chem., 273*, 21623-8. ↗

Editions

2015-05-21	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

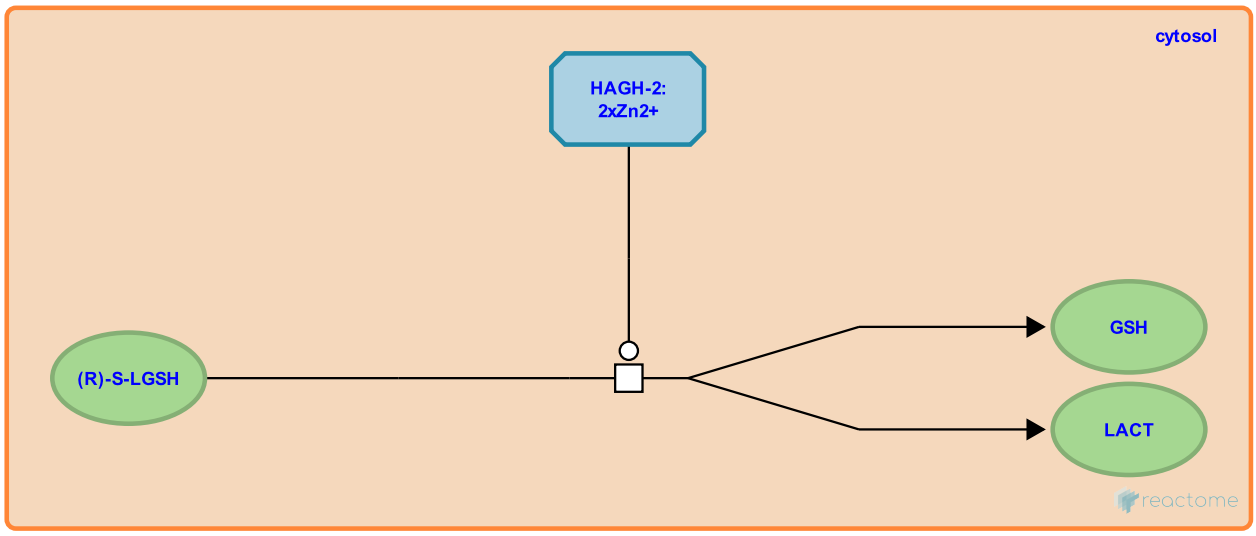
HAGH hydrolyses (R)-S-LGSH to GSH and LACT ↗

Location: Pyruvate metabolism

Stable identifier: R-HSA-6783221

Type: transition

Compartments: cytosol



In the second step of the glyoxalase system, hydroxyacylglutathione hydrolase (HAGH) catalyses the hydrolysis of (R)-S-lactoylglutathione ((R)-S-LGSH) to glutathione (GSH) and lactic acid (LACT) (Ridderstrom et al. 1996). The HAGH gene can produce two forms of the protein, form 1 is mitochondrial whereas form 2 is cytosolic (Cordell et al. 2004). HAGH is monomeric but requires two Zn2+ ions for activity (Cameron et al. 1999). This reaction completes the detoxification of methylglyoxal, a reactive byproduct of pyruvate metabolism.

Literature references

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Editions

2015-06-11	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

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