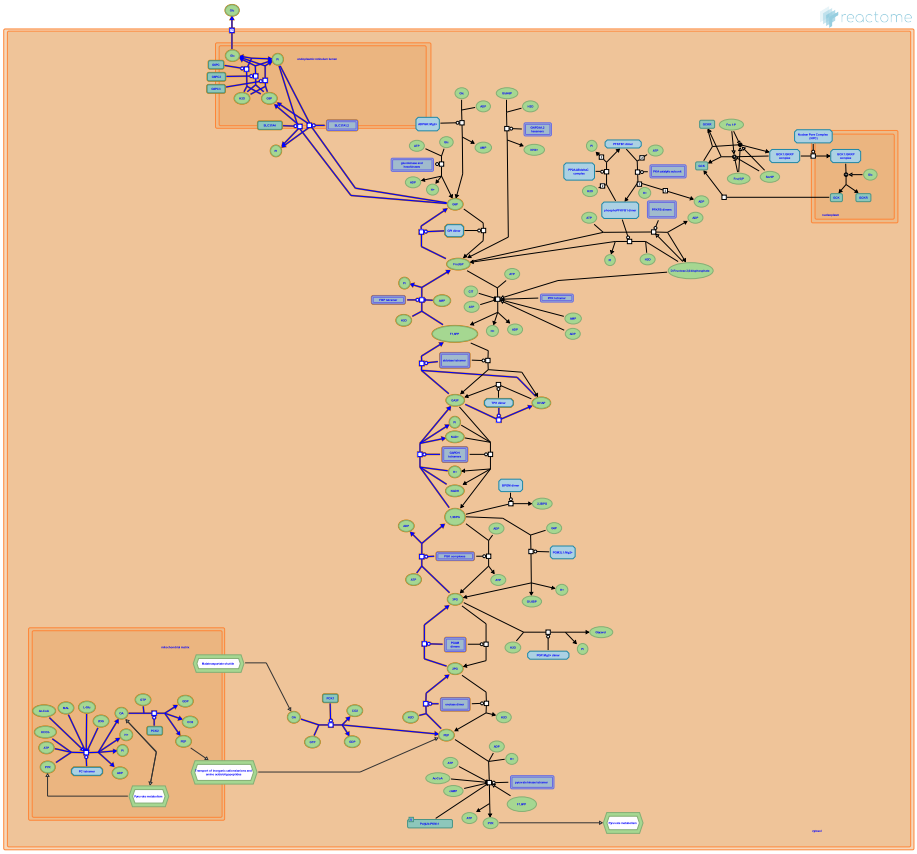
Gluconeogenesis



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30/04/2024

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.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

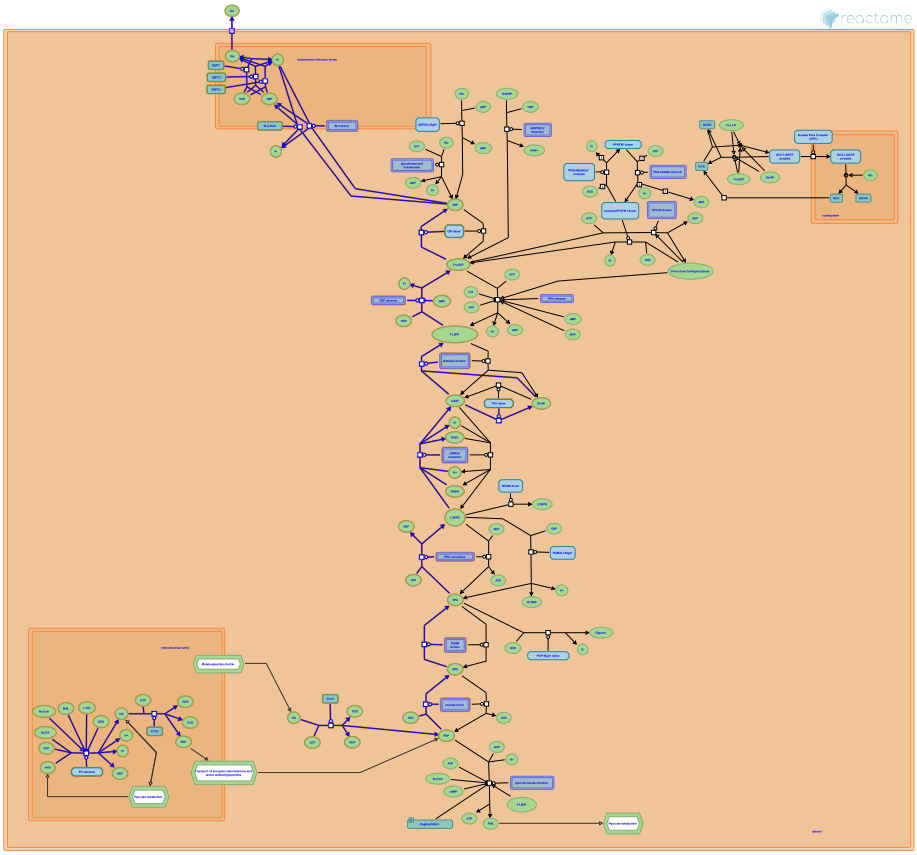
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Gluconeogenesis ↗

Stable identifier: R-HSA-70263



Gluconeogenesis converts mitochondrial pyruvate to cytosolic glucose 6 phosphate which in turn can be hydrolyzed to glucose and exported from the cell. Gluconeogenesis is confined to cells of the liver and kidney and enables glucose synthesis from molecules such as lactate and alanine and other amino acids when exogenous glucose is not available (reviewed, e.g., by Chourpiliadis & Mohiuddin 2022). Gluconeogenesis occurs in two parts: a network of reactions converts mitochondrial pyruvate to cytosolic phosphoenolpyruvate; then phosphoenolpyruvate is converted to glucose 6 phosphate in a single sequence of cytosolic reactions.

Three variants of the first part of the process are physiologically important. 1) A series of transport and transamination reactions convert mitochondrial oxaloacetate to cytosolic oxaloacetate which is converted to phosphoenolpyruvate by a hormonally regulated, cytosolic isoform of phosphoenolpyruvate carboxykinase. This variant allows regulated glucose synthesis from lactate. 2) Mitochondrial oxaloacetate is reduced to malate, which is exported to the cytosol and re oxidized to oxaloacetate. This variant provides reducing equivalents to the cytosol, needed for glucose synthesis from amino acids such as alanine and glutamine. 3) Constitutively expressed mitochondrial phosphoenolpyruvate carboxykinase catalyzes the conversion of mitochondrial oxaloacetate to phosphoenolpyruvate which may then be transported to the cytosol. The exact path followed by any one molecule of pyruvate through this reaction network is determined by the tissue in which the reactions are occurring, the source of the pyruvate, and the physiological stress that triggered gluconeogenesis.

In the second part of gluconeogenesis, cytosolic phosphoenolpyruvate, however derived, is converted to fructose 1,6 bisphosphate by reactions that are the reverse of steps of glycolysis. Hydrolysis of fructose 1,6 bisphosphate to fructose 6 phosphate is catalyzed by fructose 1,6 bisphosphatase, and fructose 6 phosphate is reversibly isomerized to glucose 6 phosphate.

In all cases, the synthesis of glucose from two molecules of pyruvate requires the generation and consumption of two reducing equivalents as cytosolic NADH + H+. For pyruvate derived from lactate (variants 1 and 3), NADH + H+ is generated with the oxidation of lactate to pyruvate in the cytosol (a reaction of pyruvate metabolism not shown in the diagram). For pyruvate derived from amino acids (variant 2), mitochondrial NADH + H+ generated by glutamate dehydrogenase (a reaction of amino acid metabolism, not shown) is used to reduce oxaloacetate to malate, which is transported to the cytosol and re oxidized, generating cytosolic NADH + H+. The synthesis of glucose from pyruvate also requires the consumption of six high energy phosphates, four from ATP and two from GTP.

Literature references

Chourpiliadis, C., Mohiuddin, SS. (2022). Biochemistry, Gluconeogenesis. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
2008-09-13	Revised	D'Eustachio, P.
2022-08-29	Revised	D'Eustachio, P.
2022-08-29	Reviewed	Hill, DP.
2024-03-06	Edited	D'Eustachio, P.

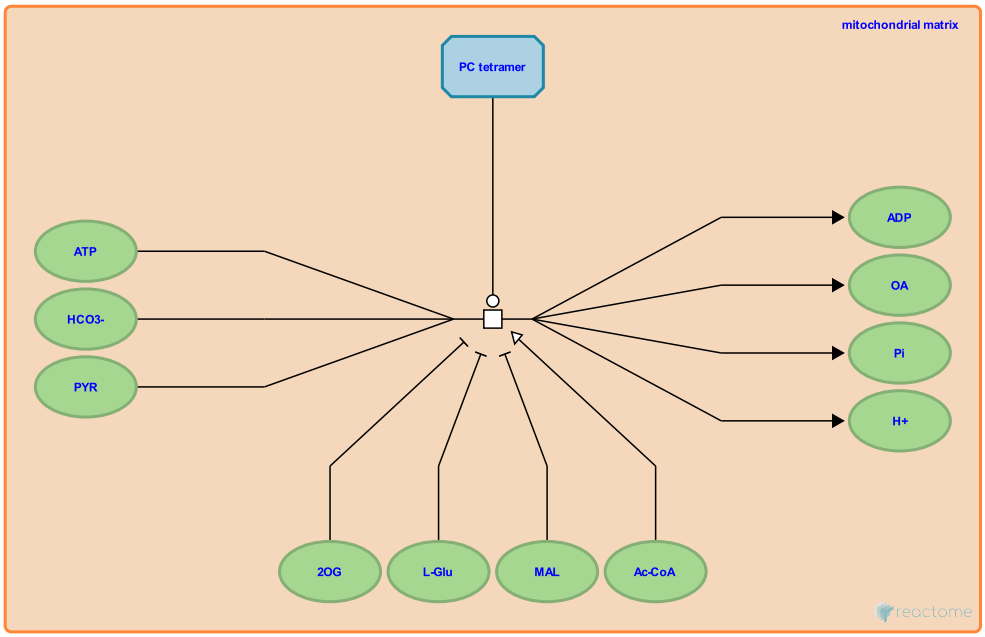
PC carboxylates PYR to OA ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-70501

Type: transition

Compartments: mitochondrial matrix



Mitochondrial pyruvate carboxylase (PC) catalyzes the irreversible reaction of pyruvate (PYR), bicarbonate (HCO3-), and ATP to form oxaloacetate (OA), ADP, phosphate, (Pi), and H+. The enzyme is biotinylated and is active as a tetramer. The protein structure and function have been characterized in detail (Jitrapakdee et al., 2008; Jitrapakdee & Wallace, 1999; Lopez-Alonso et al., 2022). The reaction proceeds in two steps, with the biotin modification carboxylated first (Wexler et al., 1998). It is highly sensitive to activation by acetyl-CoA and gets inhibited by 2-oxoglutarate, L-malate, and L-glutamate (Scrutton & White, 1974; Jitrapakdee et al., 2008). Activation of PC by acetyl-CoA produced from lipolysis and leading to excess gluconeogenesis is the central mechanism of metabolic syndrome and diabetes (reviewed in Lao-On et al., 2018). Both normal and defective forms of the human enzyme have been described, with deficiency leading to lactic acidosis and potentially intellectual disability and death (MIM:266150; Carbone & Robinson, 2003; reviewed in Marin-Valencia et al., 2010).

Followed by: PCK2 phosphorylates OA to yield PEP

Literature references

Robinson, BH., Carbone, MA. (2003). Expression and characterization of a human pyruvate carboxylase variant by retroviral gene transfer. *Biochem J, 370*, 275-282. ↗

Jitrapakdee, S., Wallace, JC. (1999). Structure, function and regulation of pyruvate carboxylase. *Biochem J, 340*, 1-16. ↗

White, MD., Scrutton, MC. (1974). Purification and properties of human liver pyruvate carboxylase. *Biochem Med, 9*, 217-92. ↗

Du, Y., Wexler, ID., Kerr, DS., Stephenson, W., Higgins, JJ., Wappner, RS. et al. (1998). Molecular characterization of pyruvate carboxylase deficiency in two consanguineous families. *Pediatr Res, 43*, 579-84. ↗

Tong, L., López-Alonso, JP., Choi, PH., Gil-Cartón, D., Lázaro, M., Valle, M. et al. (2022). CryoEM structural exploration of catalytically active enzyme pyruvate carboxylase. *Nat Commun, 13*, 6185. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
2022-08-29	Revised	D'Eustachio, P.
2022-08-29	Reviewed	Hill, DP.
2024-02-23	Reviewed	Hill, DP.

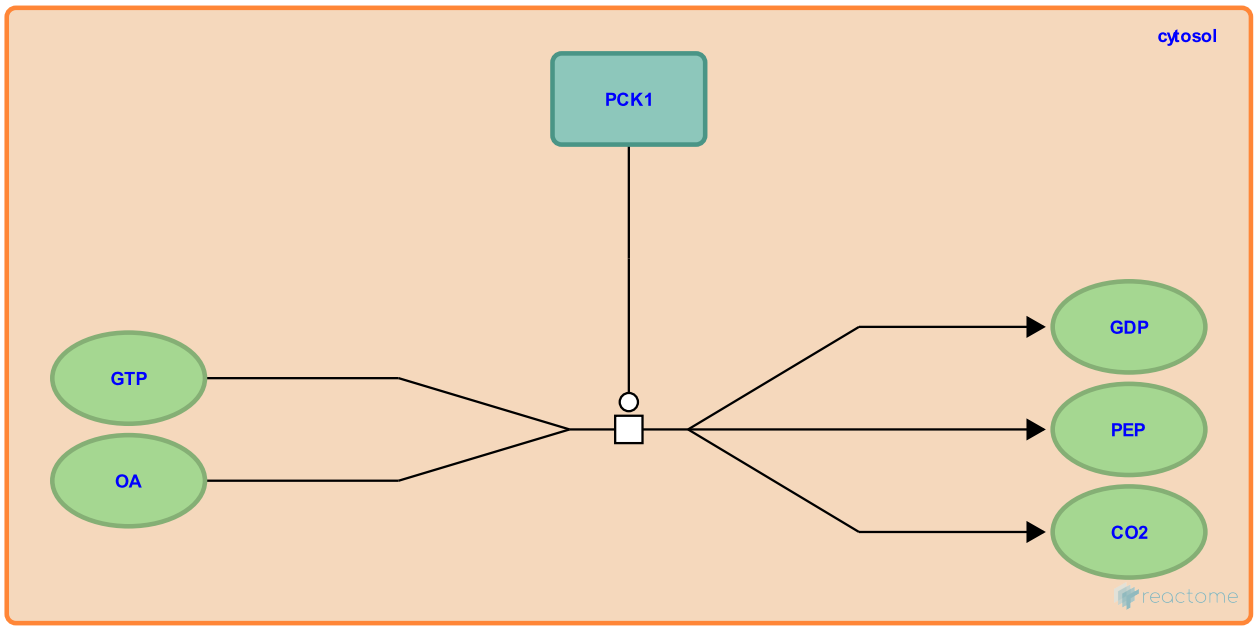
PCK1 phosphorylates OA to yield PEP ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-70241

Type: transition

Compartments: cytosol



The transfer of a high-energy phosphate bond from GTP to oxaloacetate (OA), to form phosphoenolpyruvate (PEP), GDP, and CO2, is catalyzed by cytosolic phosphoenolpyruvate carboxykinase PCK1 (Dunten et al. 2002). This reaction is irreversible under physiological conditions.

Followed by: Enolase dimers (ENO1,2,3) convert PEP to 2PG

Literature references

Michel, H., Wertheimer, SJ., Belunis, C., Crowther, R., Levin, W., Hollfelder, K. et al. (2002). Crystal structure of human cytosolic phosphoenolpyruvate carboxykinase reveals a new GTP-binding site. *J Mol Biol, 316*, 257-264. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
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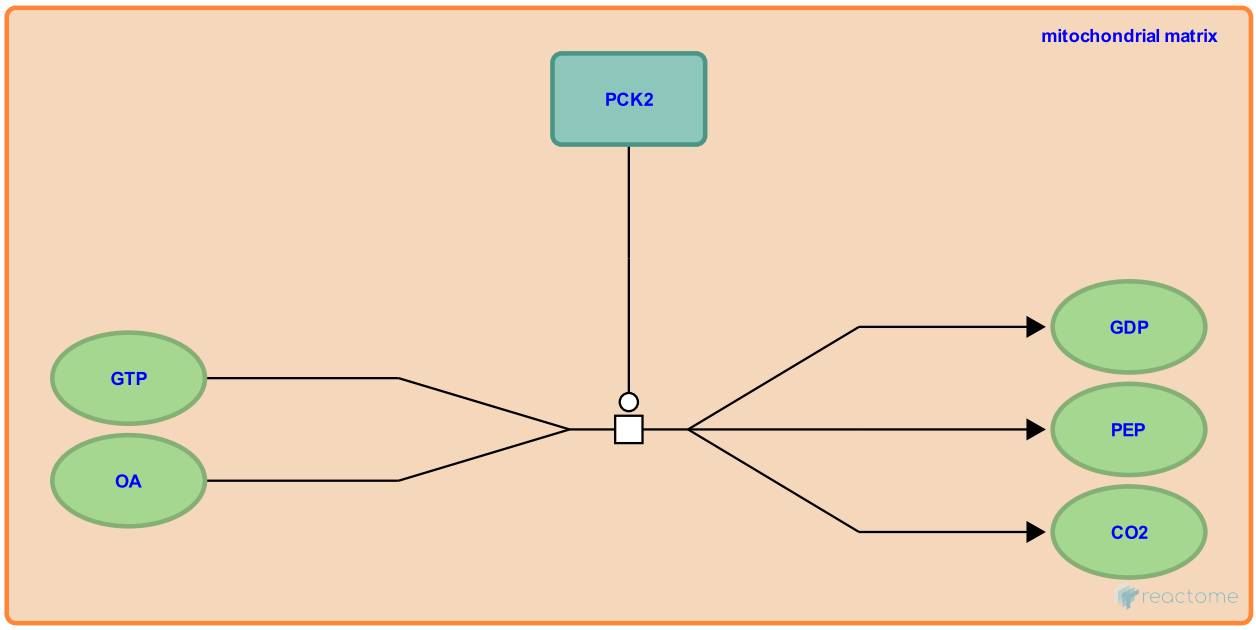
PCK2 phosphorylates OA to yield PEP ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-372819

Type: transition

Compartments: mitochondrial matrix



PCK2 (phosphoenolcarboxykinase), located in the mitochondrial matrix, catalyzes the physiologically irreversible reaction of oxaloacetate (OA) and GTP to form phosphoenolpyruvate (PEP), GDP, and CO2 (Modaressi et al. 1996, 1998).

Preceded by: PC carboxylates PYR to OA

Literature references

Christ, B., Heise, T., Modaressi, S., Jungermann, K., Bratke, J., Zahn, S. (1996). Molecular cloning, sequencing and expression of the cDNA of the mitochondrial form of phosphoenolpyruvate carboxykinase from human liver. *Biochem J, 315*, 807-14. ↗

Brechtel, K., Christ, B., Modaressi, S., Jungermann, K. (1998). Human mitochondrial phosphoenolpyruvate carboxykinase 2 gene. Structure, chromosomal localization and tissue-specific expression. *Biochem J, 333*, 359-66. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
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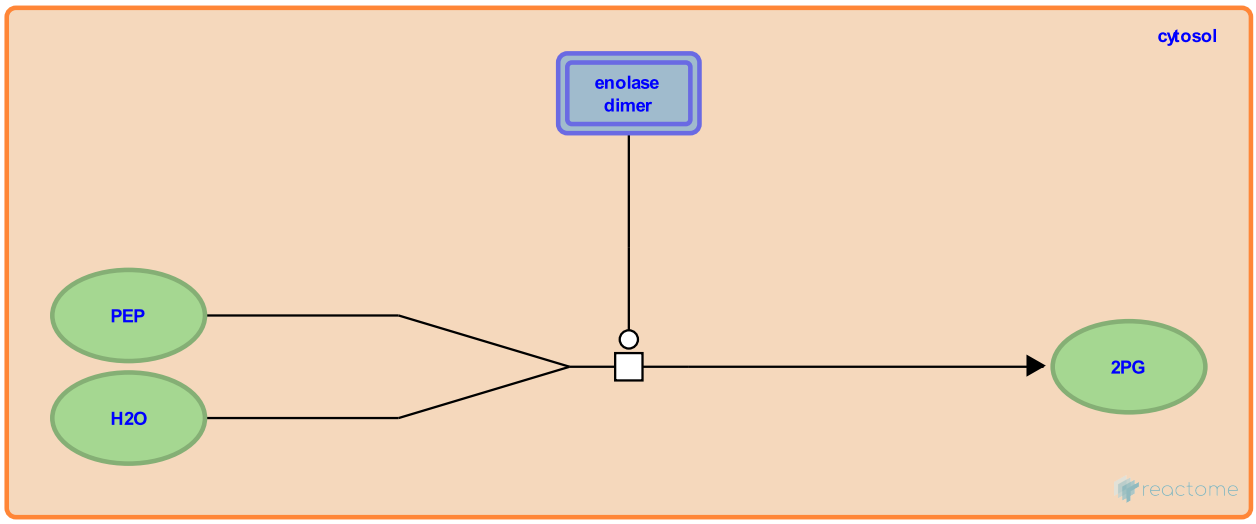
Enolase dimers (ENO1,2,3) convert PEP to 2PG ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-70494

Type: transition

Compartments: cytosol



Cytosolic enolase dimers catalyze the reversible reaction of phosphoenolpyruvate (PEP) and water to form 2-phosphoglycerate (2PG). Three enolase isozymes have been purified and biochemically characterized. The alpha isoform (ENO1) is widely expressed (Giallongo et al. 1986). The beta isoform (ENO3) is expressed in muscle. Evidence for its function in vivo in humans comes from studies of a patient in whom a point mutation in the gene encoding the enzyme was associated specifically with reduced enolase activity in muscle extracts, and with other symptoms consistent with a defect in glycolysis (Comi et al. 2001). The gamma isoform of human enolase (ENO2) is normally expressed in neural tissue. It is not known to have distinctive biochemical functions, but is of possible clinical interest as a marker of some types of neuroendocrine and lung tumors (McAleese et al. 1988). A fourth candidate isozyme, ENO4, has been identified in the human and mouse genomes. The mouse form of the gene encodes a protein with enolase activity that is expressed in sperm and whose disruption is associated with abnormal sperm morphology (Nakamura et al. 2013).

Preceded by: PCK1 phosphorylates OA to yield PEP

Followed by: PGAM dimers (PGAM1,2) isomerise 2PG to 3PG

Literature references

Dunbar, B., Day, IN., McAleese, SM., Fothergill, JE., Hinks, LJ. (1988). Complete amino acid sequence of the neuron-specific gamma isozyme of enolase (NSE) from human brain and comparison with the non-neuronal alpha form (NNE). *Eur J Biochem, 178*, 413-7. ↗

Croce, CM., Giallongo, A., Feo, S., Showe, LC., Moore, R. (1986). Molecular cloning and nucleotide sequence of a full-length cDNA for human alpha enolase. *Proc Natl Acad Sci U S A, 83*, 6741-5. ↗

Bresolin, N., Jann, S., Prelle, A., Scarlato, G., Ciscato, P., Torrente, Y. et al. (2001). Beta-enolase deficiency, a new metabolic myopathy of distal glycolysis. *Ann Neurol, 50*, 202-7. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
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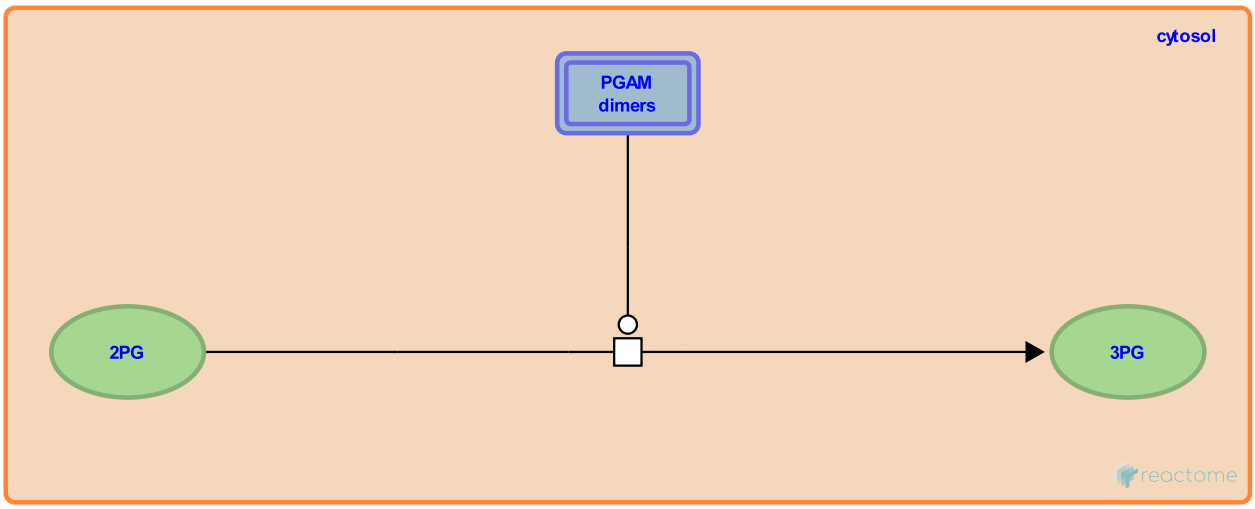
PGAM dimers (PGAM1,2) isomerise 2PG to 3PG ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-71445

Type: transition

Compartments: cytosol



Cytosolic phosphoglycerate mutase dimers (PGAM1,2) catalyze the reversible isomerisation of 2- and 3-phosphoglycerate (2PG; 3PG). There are two isoforms of this enzyme, PGAM1 (isoform B) and PGAM2 (isoform M). In the body, erythrocytes express only PGAM1, while skeletal muscle expresses only PGAM2. Other tissues express both isoforms (Omenn & Cheung 1974; Repiso et al. 2005; Tsujino et al. 1993).

Preceded by: Enolase dimers (ENO1,2,3) convert PEP to 2PG

Followed by: PGK complexes (PGK1,2) phosphorylate 3PG to form 1,3BPG

Literature references

Omenn, GS., Cheung, SC. (1974). Phosphoglycerate mutase isozyme marker for tissue differentiation in man. *Am J Hum Genet, 26*, 393-9. ↗

Baso, MJR., Repiso, A., Climent, F., Corrons, J-LV., Carreras, J. (2005). Phosphoglycerate mutase BB isoenzyme deficiency in a patient with non-spherocytic anemia: familial and metabolic studies. *Haematologica, 90*, 257-259. ↗

Fenichel, G., Sakoda, S., Tsujino, S., DiMauro, S., Shanske, S. (1993). The molecular genetic basis of muscle phosphoglycerate mutase (PGAM) deficiency. *Am J Hum Genet, 52*, 472-477. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
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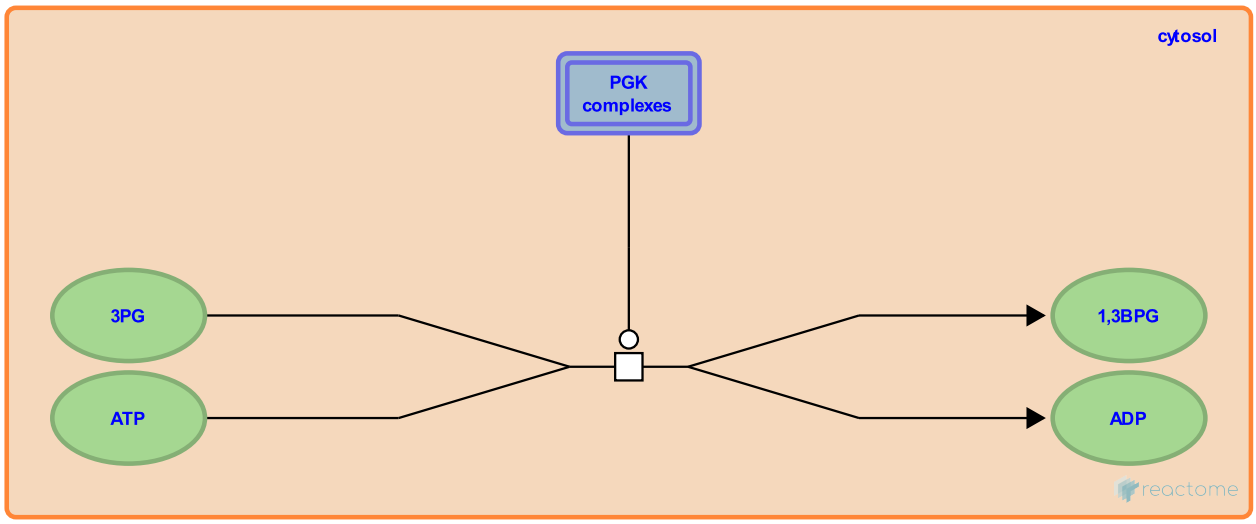
PGK complexes (PGK1,2) phosphorylate 3PG to form 1,3BPG ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-70486

Type: transition

Compartments: cytosol



Cytosolic phosphoglycerate kinase (PGK) complexed with magnesium catalyzes the reversible phosphorylation of 3-phosphoglycerate (3PG) to form 1,3-bisphosphoglycerate (1,3BPG) (Chen et al. 1976; Huang et al. 1980a, 1980b; Yoshida & Watanabe 1972).

Preceded by: PGAM dimers (PGAM1,2) isomerise 2PG to 3PG

Followed by: GAPDH tetramers reduce 1,3BPG to GA3P

Literature references

Welch, CD., Huang, IY., Yoshida, A. (1980). Complete amino acid sequence of human phosphoglycerate kinase. Cyanogen bromide peptides and complete amino acid sequence. *J Biol Chem, 255*, 6412-20. ↗

Donahue, RP., Scott, CR., Chen, SH. (1976). Characterization of phosphoglycerate kinase from human spermatozoa. *Fertil. Steril., 27*, 699-701. ↗

Watanabe, S., Yoshida, A. (1972). Human phosphoglycerate kinase. I. Crystallization and characterization of normal enzyme. *J Biol Chem, 247*, 440-5. ↗

Rubinfien, E., Huang, IY., Yoshida, A. (1980). Complete amino acid sequence of human phosphoglycerate kinase. Isolation and amino acid sequence of tryptic peptides. *J Biol Chem, 255*, 6408-11. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
2015-11-09	Revised	D'Eustachio, P.
2022-08-29	Reviewed	Hill, DP.

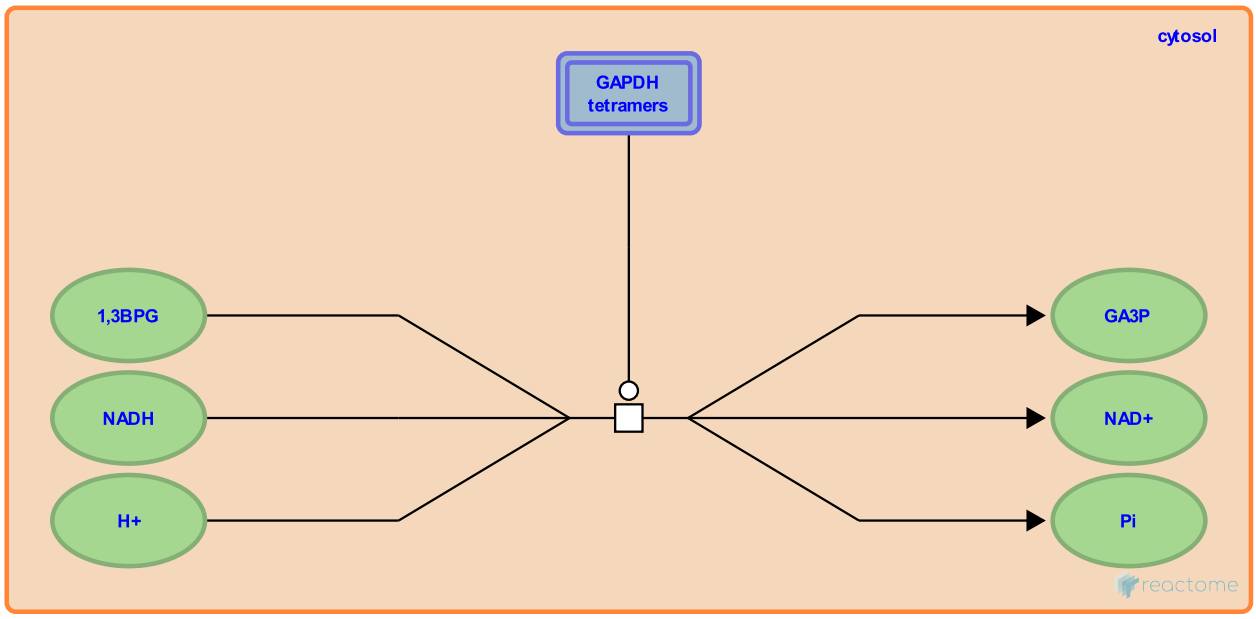
GAPDH tetramers reduce 1,3BPG to GA3P ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-70482

Type: transition

Compartments: cytosol



The reversible reduction of 1,3BPG (1,3-bisphosphoglycerate) to form G3P (glyceraldehyde-3-phosphate) is catalyzed by cytosolic GAPDH (glyceraldehyde-3-phosphate dehydrogenase) tetramer.

There are multiple human GAPDH-like pseudogenes, but only one GAPDH gene expressed in somatic tissue (Benham and Povey 1989). Consistent with this conclusion, the homogeneous enzymes purified from various human tissues had indistinguishable physical and immunochemical properties (Heinz and Freimuller 1982), and studies of human erythrocytes of various ages suggested that variant forms of the enzyme arise as a result of post-translational modifications (Edwards et al. 1976). There is, however, an authentic second isoform of GAPDH whose expression is confined to spermatogenic cells of the testis (Welch et al. 2000).

Preceded by: PGK complexes (PGK1,2) phosphorylate 3PG to form 1,3BPG

Followed by: Aldolase tetramers convert GA3P and DHAP to F1,6PP, TPI1 isomerizes GA3P to DHAP

Literature references

Eddy, EM., Bunch, DO., Mori, C., O'Brien, DA., Magyar, PL., Welch, JE. et al. (2000). Human glyceraldehyde 3-phosphate dehydrogenase-2 gene is expressed specifically in spermatogenic cells. *J Androl, 21*, 328-38. ↗

Edwards, YH., Harris, H., Clark, P. (1976). Isozymes of glyceraldehyde-3-phosphate dehydrogenase in man and other mammals. *Ann Hum Genet, 40*, 67-77. ↗

Florence, B., Alexander, M., Denaro, M., Ercolani, L. (1988). Isolation and complete sequence of a functional human glyceraldehyde-3-phosphate dehydrogenase gene. *J Biol Chem, 263*, 15335-41. ↗

Freimüller, B., Heinz, F. (1983). Glyceraldehyde-3-phosphate dehydrogenase from human tissues. *Methods Enzymol, 89*, 301-5. ↗

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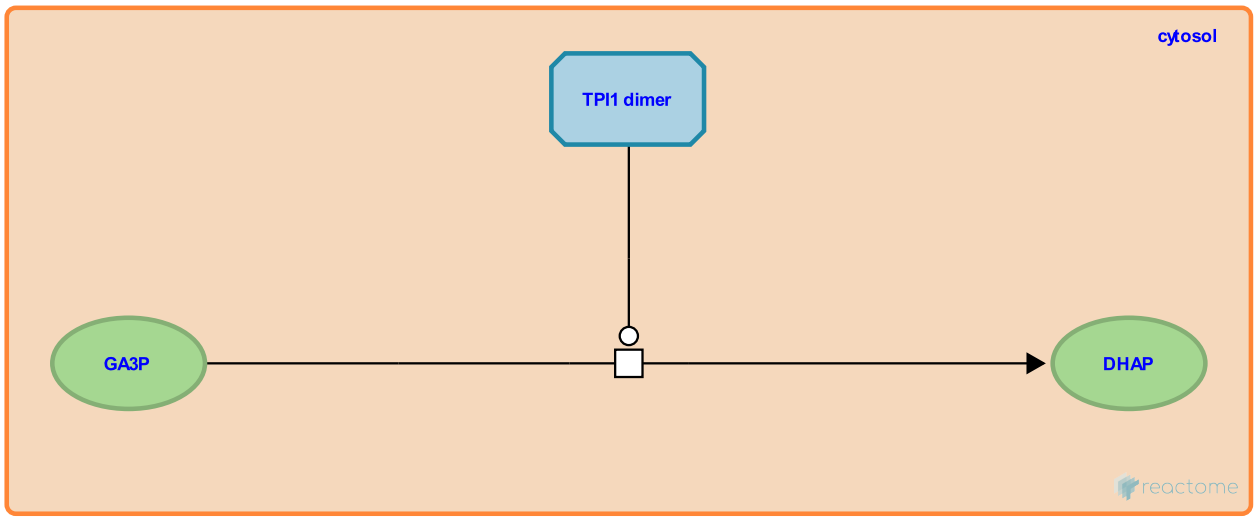
TPI1 isomerizes GA3P to DHAP ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-70481

Type: transition

Compartments: cytosol



The reversible conversion of GA3P (glyceraldehyde-3-phosphate) to DHAP (dihydroxyacetone phosphate) is catalyzed by cytosolic TPI1 (triose phosphate isomerase) (Watanabe et al. 1996; Lu et al. 1984).

Preceded by: GAPDH tetramers reduce 1,3BPG to GA3P

Followed by: Aldolase tetramers convert GA3P and DHAP to F1,6PP

Literature references

Watanabe, M., Zingg, BC., Mohrenweiser, HW. (1996). Molecular analysis of a series of alleles in humans with reduced activity at the triosephosphate isomerase locus. *Am J Hum Genet, 58*, 308-16. ↗

Gracy, RW., Yuan, PM., Lu, HS. (1984). Primary structure of human triosephosphate isomerase. *J Biol Chem, 259*, 11958-68. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
2022-08-29	Revised	D'Eustachio, P.
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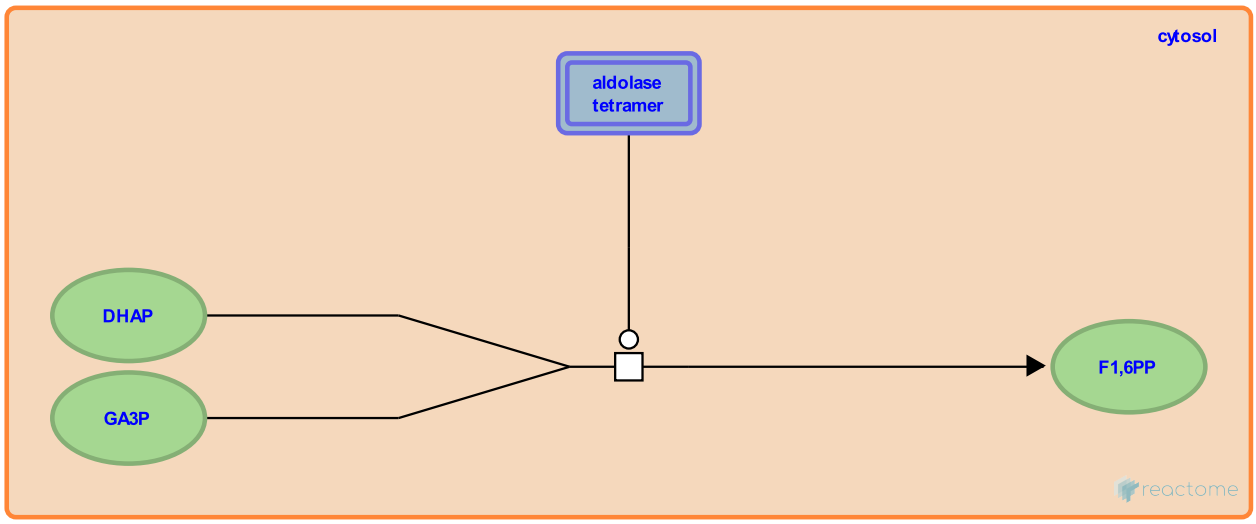
Aldolase tetramers convert GA3P and DHAP to F1,6PP ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-71495

Type: transition

Compartments: cytosol



In this freely reversible cytosolic reaction, DHAP (dihydroxyacetone phosphate) and GA3P (D-glyceraldehyde 3-phosphate) react to form F1,6PP (D-fructose 1,6-bisphosphate). The active form of aldolase, the enzyme that catalyzes the reaction, is a homotetramer. Three aldolase isozymes have been identified which differ in their patterns of expression in various adult tissues and during development but are otherwise functionally indistinguishable (Ali and Cox 1995; Dunbar and Fothergill-Gilmore 1988).

Preceded by: GAPDH tetramers reduce 1,3BPG to GA3P, TPI1 isomerizes GA3P to DHAP

Followed by: FBP tetramers hydrolyze F1,6PP to Fru(6)P

Literature references

Cox, TM., Ali, M. (1995). Diverse mutations in the aldolase B gene that underlie the prevalence of hereditary fructose intolerance. *Am J Hum Genet, 56*, 1002-5. ↗

Dunbar, B., Fothergill-Gilmore, LA. (1988). The complete amino acid sequence of human skeletal-muscle fructose-bisphosphate aldolase. *Biochem J, 249*, 779-88. ↗

Editions

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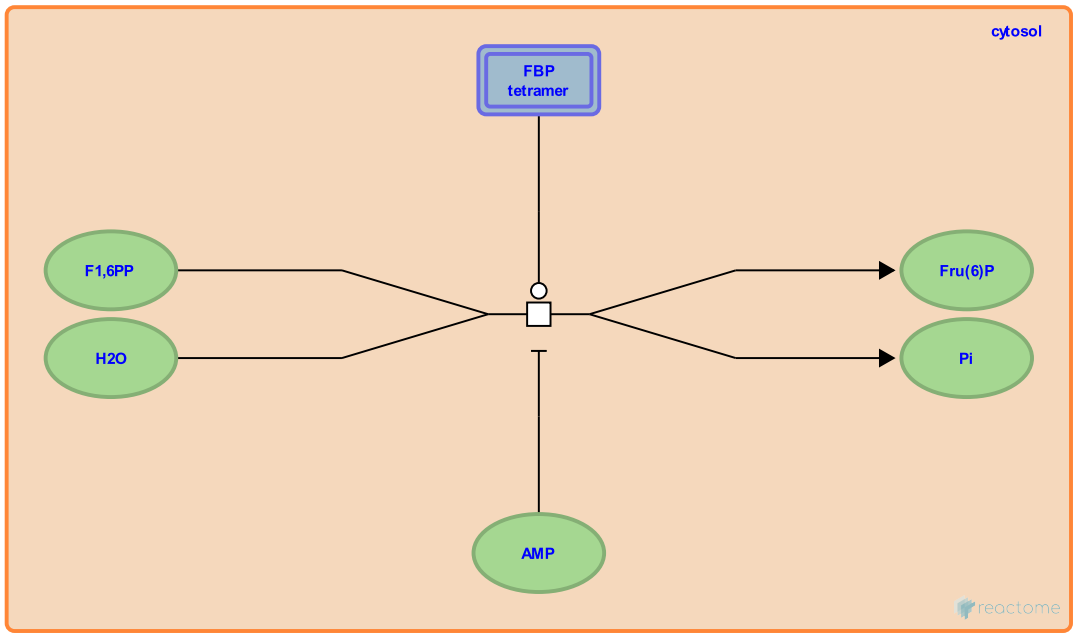
FBP tetramers hydrolyze F1,6PP to Fru(6)P ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-70479

Type: transition

Compartments: cytosol



Cytosolic FBP (fructose-1,6-bisphosphatase) tetramers catalyze the physiologically irreversible hydrolysis of F1,6PP (fructose-1,6-bisphosphate) to form Fru(6)P (fructose-6-phosphate) and Pi (orthophosphate). In the body, two isoforms of the enzyme are expressed, one ubiquitous and one muscle-specific (Kikawa et al. 1997; Tillmann and Eschrich 1998).

Preceded by: Aldolase tetramers convert GA3P and DHAP to F1,6PP

Followed by: GPI dimer isomerizes Fru(6)P to G6P

Literature references

Nakai, A., Taketo, A., Sudo, M., Yamamoto, Y., Jin, BY., Fujisawa, K. et al. (1997). Identification of genetic mutations in Japanese patients with fructose-1,6-bisphosphatase deficiency. *Am J Hum Genet, 61*, 852-861. ↗

Tillmann, H., Eschrich, K. (1998). Isolation and characterization of an allelic cDNA for human muscle fructose-1,6-bisphosphatase. *Gene, 212*, 295-304. ↗

Editions

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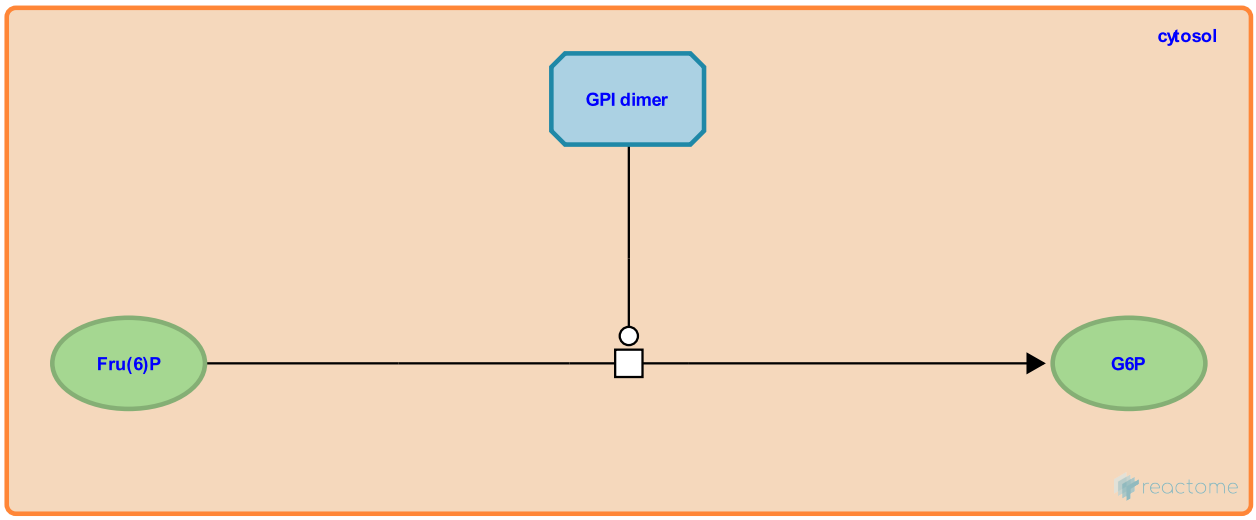
GPI dimer isomerizes Fru(6)P to G6P ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-70475

Type: transition

Compartments: cytosol



The reversible isomerization of Fru(6)P (fructose-6-phosphate) to form G6P (glucose-6-phosphate) is catalyzed by cytosolic GPI (phosphoglucose isomerase) dimer (Noltman 1972; Tsuboi et al. 1958; Xu and Beutler 1994).

Preceded by: FBP tetramers hydrolyze F1,6PP to Fru(6)P

Followed by: SLC7A4 exchanges G6P for Pi across the ER membrane

Literature references

Beutler, E., Xu, W. (1994). The characterization of gene mutations for human glucose phosphate isomerase deficiency associated with chronic hemolytic anemia. *J Clin Invest, 94*, 2326-9. ↗

Tsuboi, KK., Hudson, PB., Estrada, J. (1958). Enzymes of the human erythrocyte. IV. Phosphoglucose isomerase, purification and properties. *J Biol Chem, 231*, 19-29. ↗

Boyer, PD. (1972). Aldose-ketose isomerases, The Enzymes, 3rd ed. *Academic Press*, 271-354.

Editions

2003-02-05	Authored	Schmidt, EE.
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2022-08-29	Reviewed	Hill, DP.

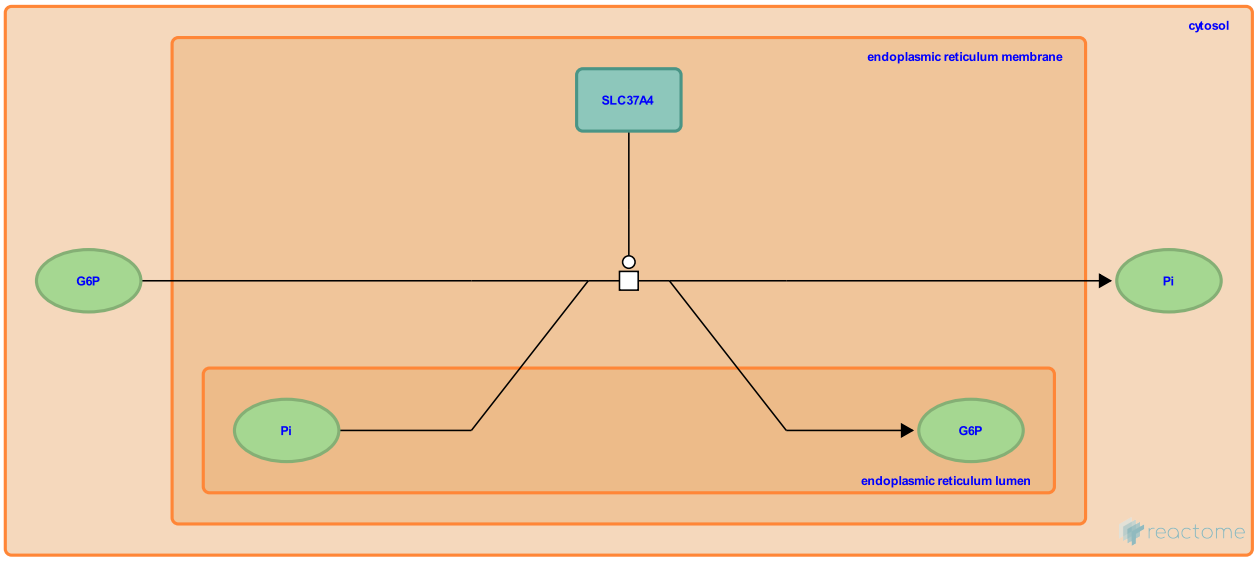
SLC7A4 exchanges G6P for Pi across the ER membrane ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-198513

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen, cytosol



The SLC37A4 transport protein in the endoplasmic reticulum membrane mediates the exchange of cytosolic G6P (glucose-6-phosphate) and Pi (orthophosphate) from the endoplasmic reticulum lumen. Defects in this transporter are associated with glycogen storage disease type Ib (Gerin et al. 1997; Chen et al. 2008; Veiga-da-Cunha et al. 1998).

Preceded by: GPI dimer isomerizes Fru(6)P to G6P

Followed by: G6PC hydrolyzes G6P to Glc and Pi (liver)

Literature references

Collet, JF., Achouri, Y., Gerin, I., Veiga-da-Cunha, M., Van Schaftingen, E. (1997). Sequence of a putative glucose 6-phosphate translocase, mutated in glycogen storage disease type Ib. *FEBS Lett, 419*, 235-238. ↗

Chou, JY., Pan, CJ., Mansfield, BC., Nandigama, K., Ambudkar, SV., Chen, SY. (2008). The glucose-6-phosphate transporter is a phosphate-linked antiporter deficient in glycogen storage disease type Ib and Ic. *FASEB J., 22*, 2206-13. ↗

Fenske, CD., Chen, Y-T., Leonard, JV., Schweitzer, S., de Barsy, T., Maire, I. et al. (1998). A gene on chromosome 11q23 coding for a putative glucose- 6-phosphate translocase is mutated in glycogen-storage disease types Ib and Ic. *Am. J. Hum. Genet., 63*, 976-83. ↗

Editions

2007-06-22	Authored	D'Eustachio, P.
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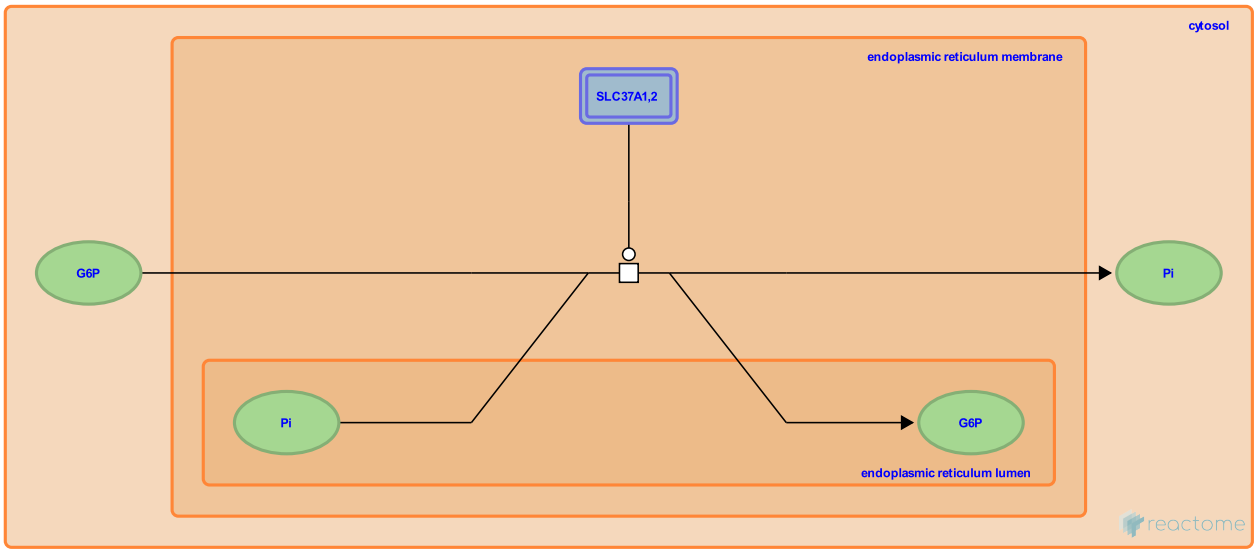
SLC37A1, SLC37A2 exchange G6P for Pi across the ER membrane ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-3257122

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen, cytosol



The SLC37A1 and SLC37A2 transport proteins mediate the exchange of G6P (glucose-6-phosphate) and Pi (orthophosphate) across lipid bilayer membranes in vitro, and both proteins are located in the endoplasmic reticulum membrane. Their physiological function, however, is unknown (Pan et al. 2011; Chou et al. 2013).

Literature references

Chou, JY., Pan, CJ., Mansfield, BC., Chen, SY., Lin, SR., Jun, HS. (2011). SLC37A1 and SLC37A2 are phosphate-linked, glucose-6-phosphate antiporters. *PLoS ONE, 6*, e23157. ↗

Chou, JY., Sik Jun, H., Mansfield, BC. (2013). The SLC37 family of phosphate-linked sugar phosphate antiporters. *Mol. Aspects Med., 34*, 601-11. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
2013-04-09	Authored, Edited	D'Eustachio, P.
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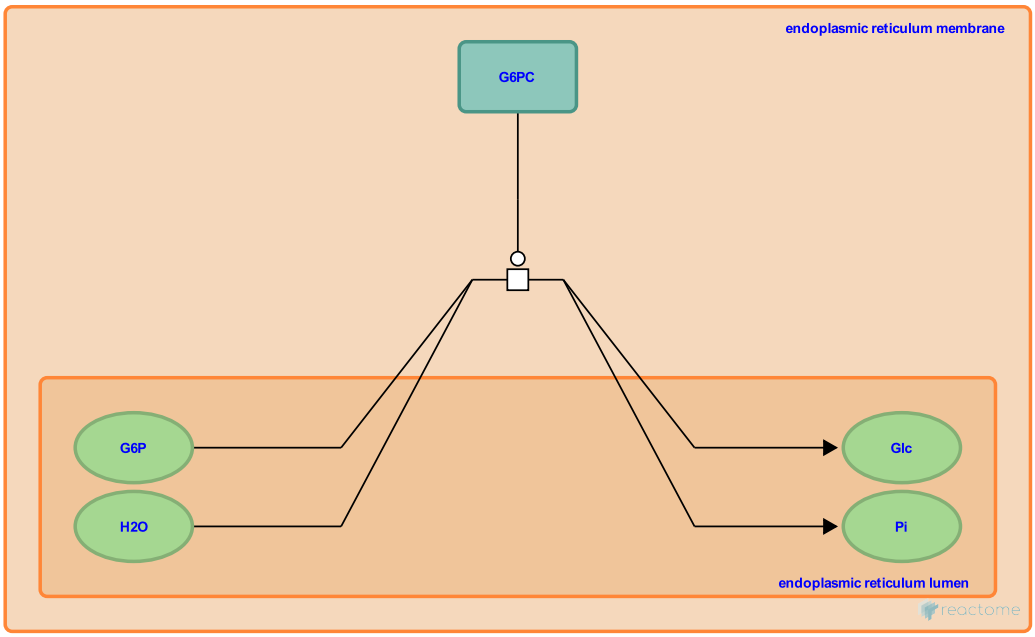
G6PC hydrolyzes G6P to Glc and Pi (liver) ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-71825

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Glucose-6-phosphatase (G6PC) associated with the inner face of the endoplasmic reticulum membrane catalyzes the hydrolysis of glucose-6-phosphate (G6P) to glucose (Glc) and orthophosphate (Pi). This reaction is essentially irreversible (Lei et al. 1993, Ghosh et al. 2002). Defects in G6PC are the cause of glycogen storage disease type 1a (Lei et al. 1993, 1995, Chou and Mansfield 2008).

Preceded by: SLC7A4 exchanges G6P for Pi across the ER membrane

Followed by: Efflux of Glc from the endoplasmic reticulum

Literature references

Chou, JY., Chen, Y-T., Lei, K-J., Ou, HC-Y., McConkie-Rosell, A., Pan, LY. et al. (1995). Genetic basis of glycogen storage disease type 1a: Prevalent mutations at the glucose-6-phosphatase locus. *Am J Hum Genet, 57*, 766-771. ↗

Chou, JY., Shieh, JJ., Sun, MS., Pan, CJ., Ghosh, A. (2002). The catalytic center of glucose-6-phosphatase. HIS176 is the nucleophile forming the phosphohistidine-enzyme intermediate during catalysis. *J. Biol. Chem., 277*, 32837-42 . ↗

Chou, JY., Mansfield, BC. (2008). Mutations in the glucose-6-phosphatase-alpha (G6PC) gene that cause type Ia glycogen storage disease. *Hum. Mutat., 29*, 921-30. ↗

Chou, JY., Sidbury, JB., Lei, K-J., Pan, CJ., Shelly, LL. (1993). Mutations in the glucose-6-phosphatase gene that cause glycogen storage disease type 1a. *Science, 262*, 580-3. ↗

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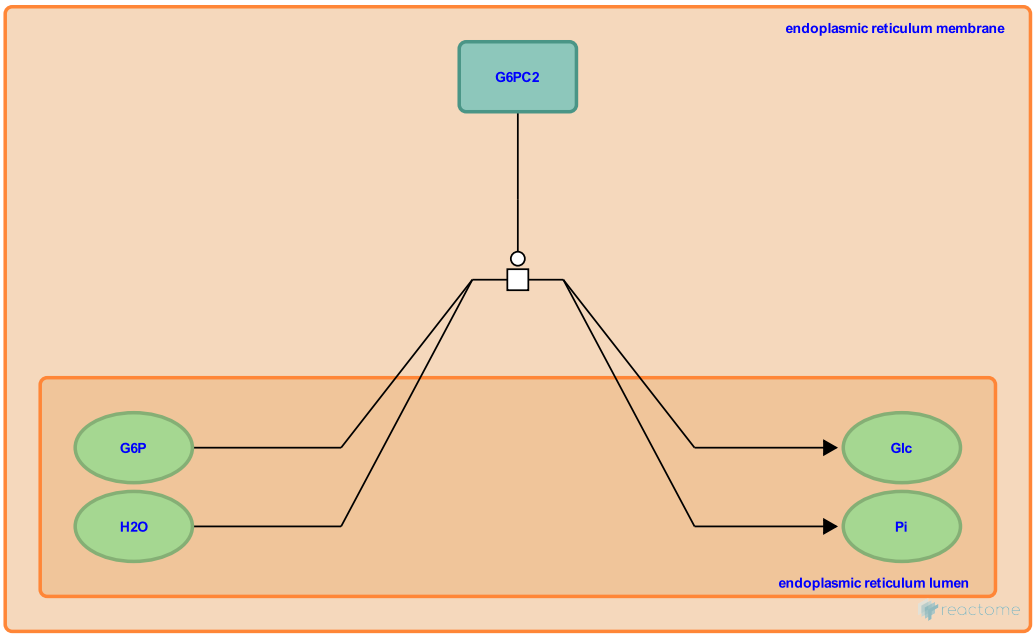
G6PC2 hydrolyzes G6P to form Glc and Pi (islet) ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-3266566

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



G6PC2 (Glucose-6-phosphatase 2), associated with the endoplasmic reticulum membrane catalyzes the hydrolysis of glucose-6-phosphate (G6P) to glucose (Glc) and orthophosphate (Pi). This reaction is essentially irreversible. This enzyme is expressed in islet cells of the pancreas (Petrolonis et al. 2004).

Literature references

Jain, S., Prack, AE., An, WF., Fish, SM., Tartaglia, LA., Tummino, PJ. et al. (2004). Enzymatic characterization of the pancreatic islet-specific glucose-6-phosphatase-related protein (IGRP). *J Biol Chem, 279*, 13976-83. ↗

Editions

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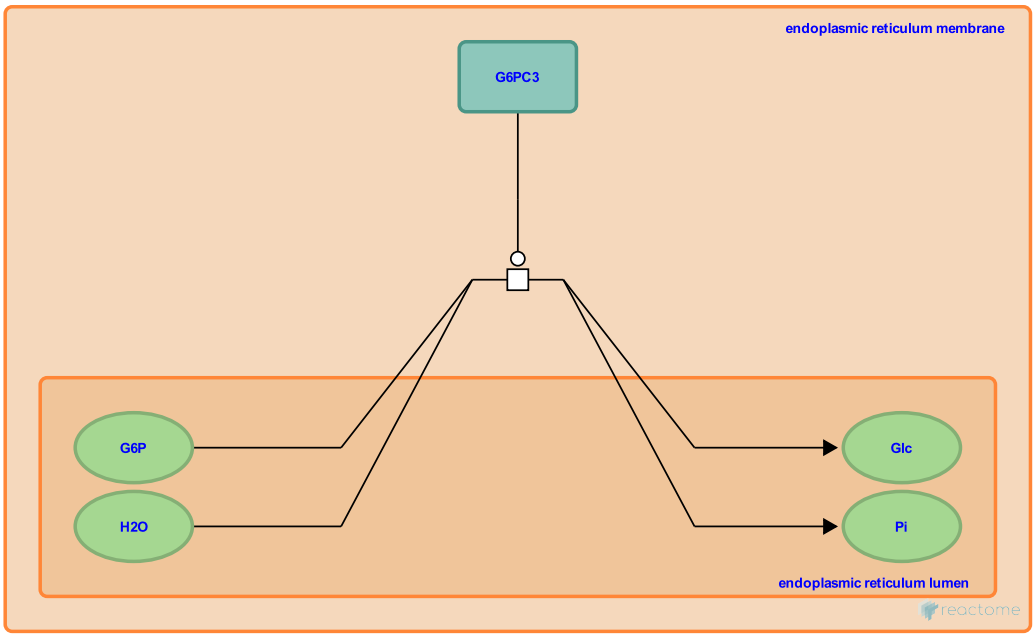
G6PC3 hydrolyzes G6P to form Glc and Pi (ubiquitous) ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-3262512

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Glucose-6-phosphatase 3 (G6PC3) associated with the endoplasmic reticulum membrane catalyzes the hydrolysis of glucose-6-phosphate (G6) to glucose (Glc) and orthophosphate (Pi). This reaction is essentially irreversible (Guionie et al. 2003; Ghosh et al. 2004). In the body, this enzyme is ubiquitously expressed; mutations that inactivate it are associated with severe congenital neutropenia (but not with fasting hypoglycemia or lactic acidemia) (Boztug et al. 2009).

Literature references

Klein, C., Kratz, C., Salzer, U., Brandes, G., Mönkemöller, K., Germeshausen, M. et al. (2009). A syndrome with congenital neutropenia and mutations in G6PC3. *N. Engl. J. Med., 360*, 32-43. ↗

Guionie, O., Clottes, E., Burchell, A., Stafford, K. (2003). Identification and characterisation of a new human glucose-6-phosphatase isoform. *FEBS Lett, 551*, 159-64. ↗

Chou, JY., Shieh, JJ., Pan, CJ., Ghosh, A. (2004). Histidine 167 is the phosphate acceptor in glucose-6-phosphatase-beta forming a phosphohistidine enzyme intermediate during catalysis. *J. Biol. Chem., 279*, 12479-83. ↗

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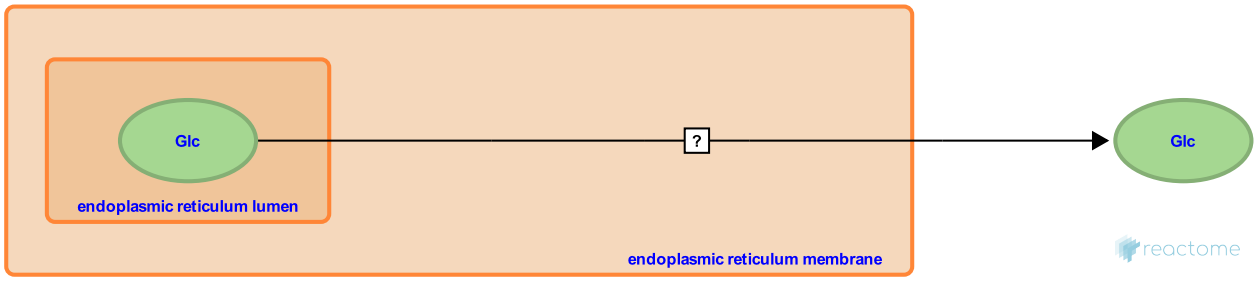
Efflux of Glc from the endoplasmic reticulum ↗

Location: Gluconeogenesis

Stable identifier: R-HSA-198458

Type: uncertain

Compartments: endoplasmic reticulum membrane, plasma membrane, extracellular region, endoplasmic reticulum lumen, cytosol



Glucose (Glc) generated within the endoplasmic reticulum is exported from the cell. Several mechanisms for this transport process have been proposed but experimental data remain incomplete and contradictory (e.g., Hosokawa and Thorens 2002; Fehr et al. 2005; Van Schaftingen and Gerin 2002).

Preceded by: G6PC hydrolyzes G6P to Glc and Pi (liver)

Literature references

Takanaga, H., Ehrhardt, DW., Frommer, WB., Fehr, M. (2005). Evidence for high-capacity bidirectional glucose transport across the endoplasmic reticulum membrane by genetically encoded fluoresence resonance energy transfer nanosensors. *Mol Cell Biol, 25*, 11102-11112. ↗

Gerin, I., Van Schaftingen, E. (2002). The glucose-6-phosphatase system. *Biochem J, 362*, 513-532. ↗

Hosokawa, M., Thorens, B. (2002). Glucose release from GLUT2-null hepatocytes: characterization of a major and a minor pathway. *Am J Physiol Endocrinol Metab, 282*, E794-E801. ↗

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2007-06-22	Authored	D'Eustachio, P.
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