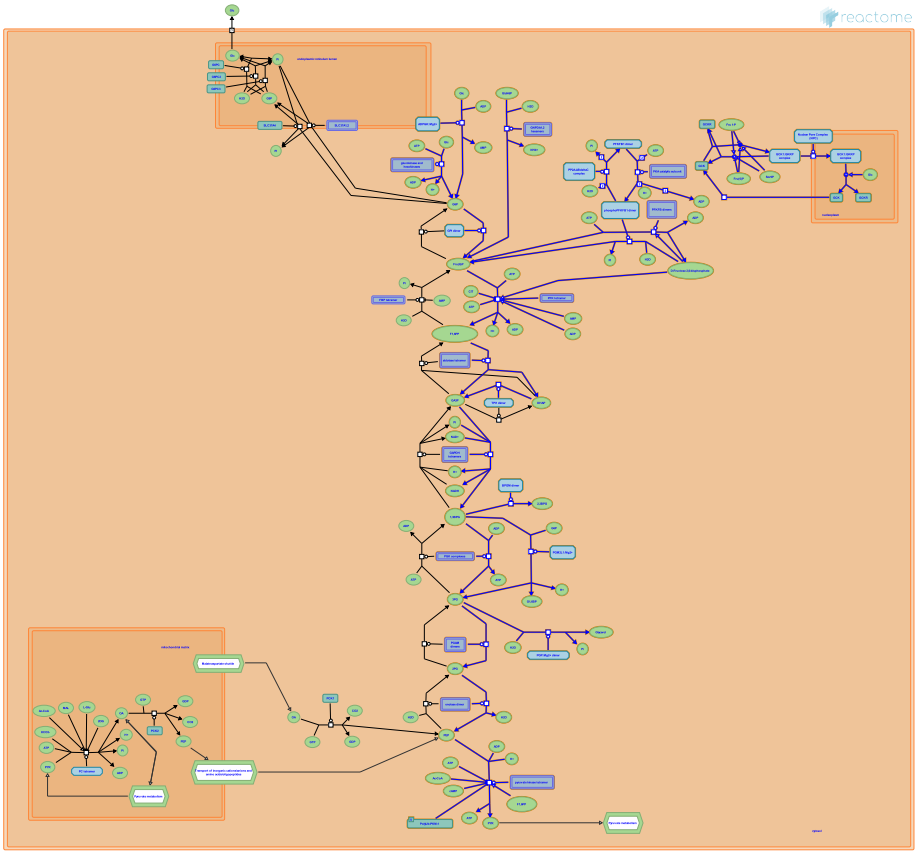
Glycolysis



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16/05/2024

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. ↗

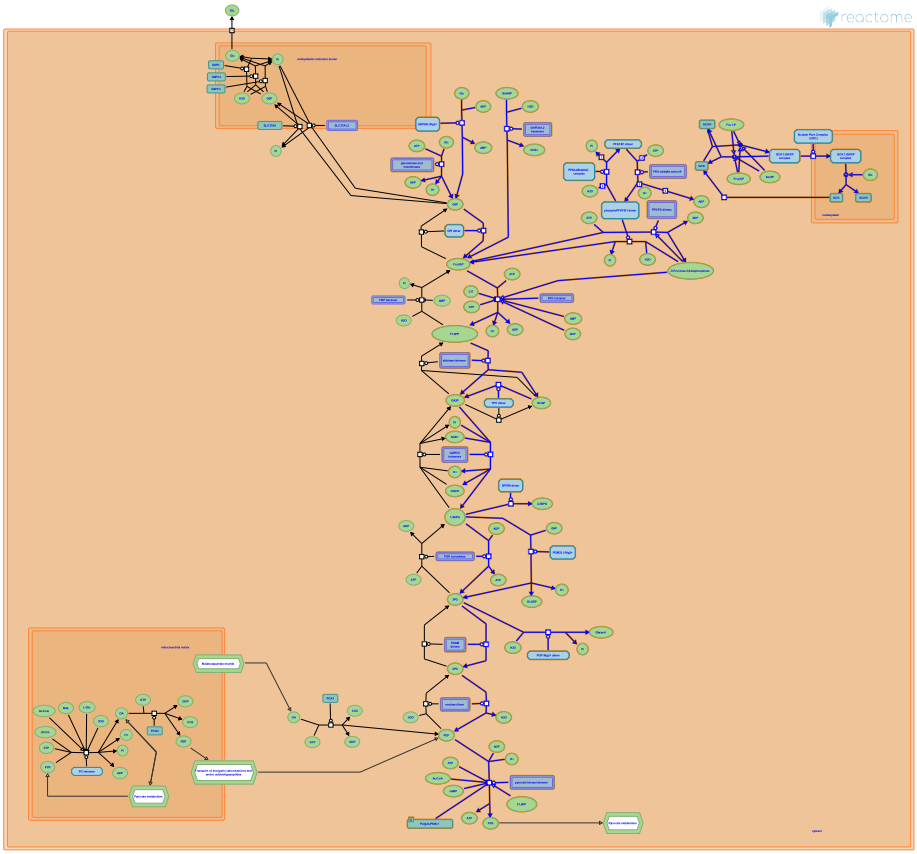
Reactome database release: 88

This document contains 3 pathways and 15 reactions (see Table of Contents)

Glycolysis ↗

Stable identifier: R-HSA-70171

Compartments: cytosol



The reactions of glycolysis (e.g., van Wijk and van Solinge 2005) convert glucose 6-phosphate to pyruvate. The entire process is cytosolic. Glucose 6-phosphate is reversibly isomerized to form fructose 6-phosphate. Phosphofructokinase 1 catalyzes the physiologically irreversible phosphorylation of fructose 6-phosphate to form fructose 1,6-bisphosphate. In six reversible reactions, fructose 1,6-bisphosphate is converted to two molecules of phosphoenolpyruvate and two molecules of NAD+ are reduced to NADH + H+. Each molecule of phosphoenolpyruvate reacts with ADP to form ATP and pyruvate in a physiologically irreversible reaction. Under aerobic conditions the NADH +H+ can be reoxidized to NAD+ via electron transport to yield additional ATP, while under anaerobic conditions or in cells lacking mitochondria NAD+ can be regenerated via the reduction of pyruvate to lactate.

Literature references

van Wijk, R., van Solinge, WW. (2005). The energy-less red blood cell is lost: erythrocyte enzyme abnormalities of glycolysis. *Blood, 106*, 4034-42. ↗

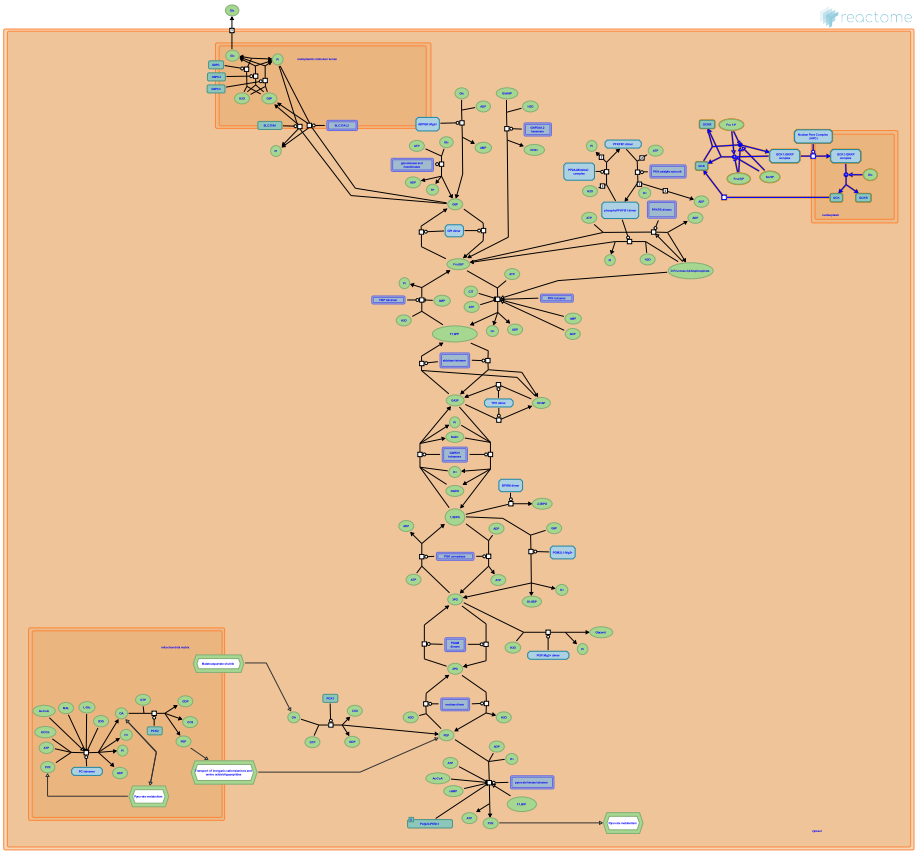
Editions

2003-01-28	Authored	Schmidt, EE.
2009-12-17	Revised	D'Eustachio, P.

Regulation of Glucokinase by Glucokinase Regulatory Protein ↗

Location: Glycolysis

Stable identifier: R-HSA-170822



Glucokinase (GCK1) is negatively regulated by glucokinase regulatory protein (GKRP), which reversibly binds the enzyme to form an inactive complex. Binding is stimulated by fructose 6-phosphate and sorbitol 6-phosphate (hence high concentrations of these molecules tend to reduce GCK1 activity) and inhibited by fructose 1-phosphate (hence a high concentration of this molecule tends to increase GCK1 activity). Once formed, the complex is translocated to the nucleus. In the presence of high glucose concentrations, the nuclear GCK1:GKRP complex dissociates, freeing GCK1 to return to the cytosol. The free GKRP is thought also to return to the cytosol under these conditions, but this return has not been confirmed experimentally. Possible physiological roles for this sequestration process are to decrease futile cycling between glucose and glucose 6 phosphate in hepatocytes under low-glucose conditions, and to decrease the lag between a rise in intracellular glucose levels and the onset of glucose phosphorylation in both hepatocytes and pancreatic beta cells (Brocklehurst et al. 2004; Shiota et al. 1999).

Literature references

Magnuson, MA., Grimsby, J., Shiota, C., Coffey, J., Grippo, JF. (1999). Nuclear import of hepatic glucokinase depends upon glucokinase regulatory protein, whereas export is due to a nuclear export signal sequence in glucokinase. *J Biol Chem, 274*, 37125-30. ↗

Brocklehurst, KJ., Agius, L., Davies, RA. (2004). Differences in regulatory properties between human and rat glucokinase regulatory protein. *Biochem J, 378*, 693-7. ↗

Editions

2006-02-20	Edited	D'Eustachio, P.
2009-12-12	Revised	D'Eustachio, P.

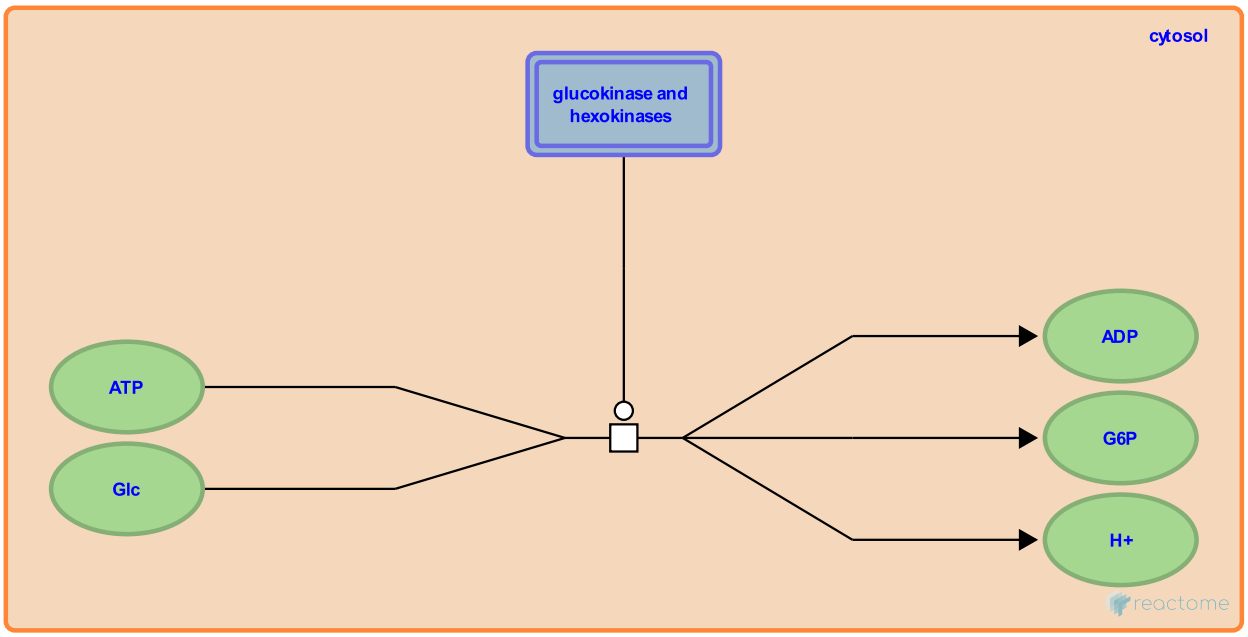
HK1,2,3,GCK,HKDC1 phosphorylate Glc to form G6P ↗

Location: Glycolysis

Stable identifier: R-HSA-70420

Type: transition

Compartments: cytosol



Cytosolic glucokinase and the three isoforms of hexokinase catalyze the irreversible reaction of glucose and ATP to form glucose 6 phosphate and ADP. In the body glucokinase is found only in hepatocytes and pancreatic beta cells. Glucokinase and the hexokinase enzymes differ in that glucokinase has a higher Km than the hexokinases and is less readily inhibited by the reaction product. As a result, glucokinase should be inactive in the fasting state when glucose concentrations are low but in the fed state should have an activity proportional to glucose concentration. These features are thought to enable efficient glucose uptake and retention in the liver, and to function as a sensor of glucose concentration coupled to insulin release in pancreatic beta cells (Thorens 2001). Glucokinase mutations are associated with MODY2, a heritable early onset form of type II diabetes (Tanizawa et al. 1991; Takeda et al. 1993). Three human hexokinase enzymes, which differ in their expression patterns have been characterized, HK1 (Aleshin et al. 1998), HK2 (Lehto et al. 1995), and HK3 (Rijksen at al. 1982).

An additional gene product, HKDC1, although not classically associated with glycolysis in adult tissues, has hexokinase activity in vitro and may have a role in glucose homeostasis during embryonic development (Guo et al. 2015; Pusik et al. 2019; Zapater et al. 2022). HKDC1 has therefore been annotated here as a candidate member of the set of enzymes that mediates glucose phosphorylation.

Followed by: PGM2L1:Mg2+ phosphorylates G6P to G1,6BP, alpha-D-glucose 6-phosphate <=> D-fructose 6-phosphate

Literature references

Le Beau, MM., Lehto, M., Laurila, E., Eriksson, KF., Bell, GI., Huang, X. et al. (1995). Human hexokinase II gene: exon-intron organization, mutation screening in NIDDM, and its relationship to muscle hexokinase activity. *Diabetologia, 38*, 1466-74. ↗

Welling, CM., Tanizawa, Y., Koranyi, LI., Permutt, MA. (1991). Human liver glucokinase gene: cloning and sequence determination of two alternatively spliced cDNAs. *Proc Natl Acad Sci U S A, 88*, 7294-7. ↗

Gidh-Jain, M., Vionnet, N., Velho, G., Pilkis, SJ., Stoffel, M., Cohen, D. et al. (1993). Structure/function studies of human beta-cell glucokinase. Enzymatic properties of a sequence polymorphism, mutations associated with diabetes, and other site-directed mutants. *J Biol Chem, 268*, 15200-4. ↗

Aleshin, AE., Bourenkov, GP., Bartunik, HD., Fromm, HJ., Zeng, C., Honzatko, RB. (1998). The mechanism of regulation of hexokinase: new insights from the crystal structure of recombinant human brain hexokinase complexed with glucose and glucose-6-phosphate. *Structure, 6*, 39-50. ↗

Cordoba-Chacon, J., Terry, AR., Hay, N., Pusec, CM., Khan, MW., Ding, X. et al. (2019). Hepatic HKDC1 Expression Contributes to Liver Metabolism. *Endocrinology, 160*, 313-330. ↗

Editions

2009-12-12	Revised	D'Eustachio, P.
2022-11-17	Revised	D'Eustachio, P.
2022-11-18	Reviewed	Hill, DP.

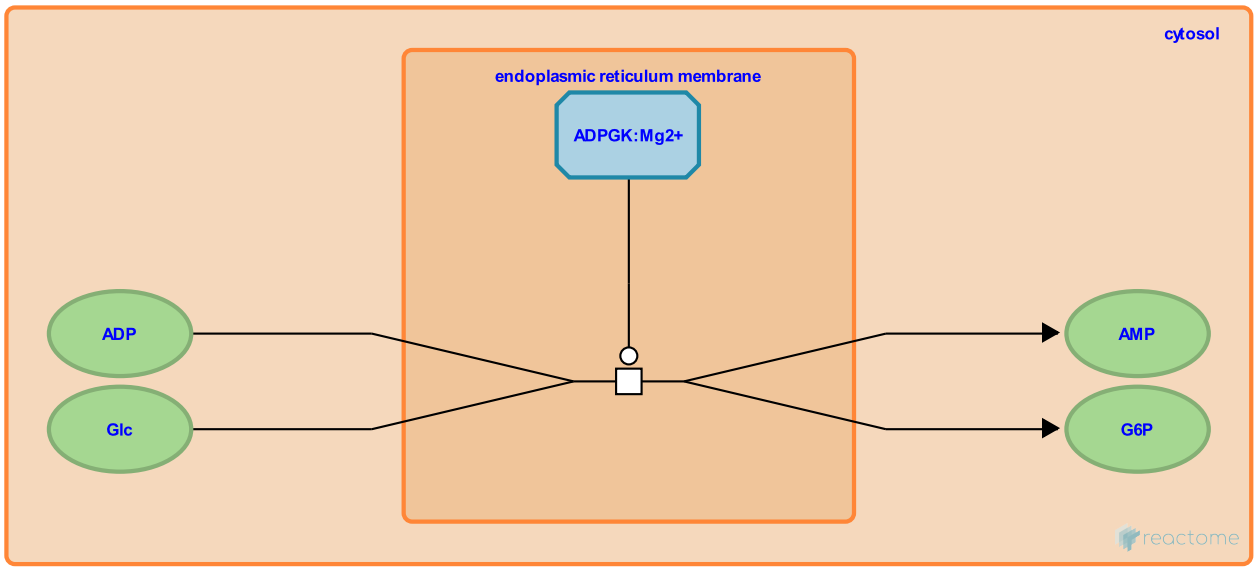
ADPGK:Mg2+ phosphorylates Glc to G6P ↗

Location: Glycolysis

Stable identifier: R-HSA-5696021

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Glucose phosphorylation is a central event in cellular metabolism. ADP-dependent glucokinase (ADPGK) can phosphorylate glucose (Glc) using ADP as the phosphate donor to glucose 6-phopshate (G6P). To date, it has not been established whether this phosphorylation supports a significant role in priming glucose for a metabolic fate other than glycolysis (Richter et al. 2012). Stdies of metabolic changes during T cell activation suggest a role for it there (Kaminski et al. 2012).

Followed by: alpha-D-glucose 6-phosphate <=> D-fructose 6-phosphate

Literature references

Stowell, KM., Richter, S., Richter, JP., Sutherland-Smith, AJ., Mehta, SY., Wilson, WR. et al. (2012). Expression and role in glycolysis of human ADP-dependent glucokinase. *Mol. Cell. Biochem., 364*, 131-45. ↗

Gülow, K., Grigaravičius, P., Opp, S., Ruppert, T., Grudnik, P., Kamiński, MM. et al. (2012). T cell activation is driven by an ADP-dependent glucokinase linking enhanced glycolysis with mitochondrial reactive oxygen species generation. *Cell Rep, 2*, 1300-15. ↗

Editions

2015-05-27	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

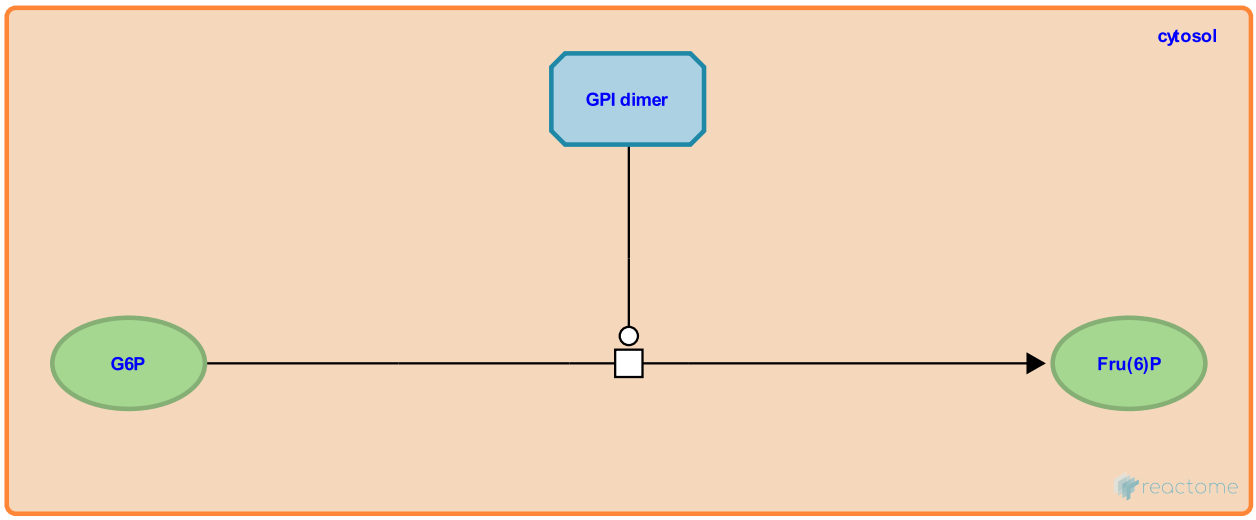
alpha-D-glucose 6-phosphate <=> D-fructose 6-phosphate ↗

Location: Glycolysis

Stable identifier: R-HSA-70471

Type: transition

Compartments: cytosol



Cytosolic phosphoglucose isomerase catalyzes the reversible interconversion of glucose 6-phosphate and fructose 6-phosphate (Tsuboi et al. 1958; Noltmann 1972; Bloxham and Lardy 1973). The active form of the enzyme is a homodimer (Read et al. 2001). Mutations in the enzyme are associated with hemolytic anemia (Xu and Beutler 1994).

Preceded by: HK1,2,3,GCK,HKDC1 phosphorylate Glc to form G6P, ADPGK:Mg2+ phosphorylates Glc to G6P

Followed by: D-fructose 6-phosphate + ATP => D-fructose 1,6-bisphosphate + ADP

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.

Muirhead, H., Read, J., Li, X., Davies, C., Chirgwin, J., Pearce, J. (2001). The crystal structure of human phosphoglucose isomerase at 1.6 A resolution: implications for catalytic mechanism, cytokine activity and haemolytic anaemia. *J Mol Biol, 309*, 447-63. ↗

Boyer, PD. (1973). Phosphofructokinase, The Enzymes, 3rd ed. 239-278.

Editions

2009-12-17	Revised	D'Eustachio, P.

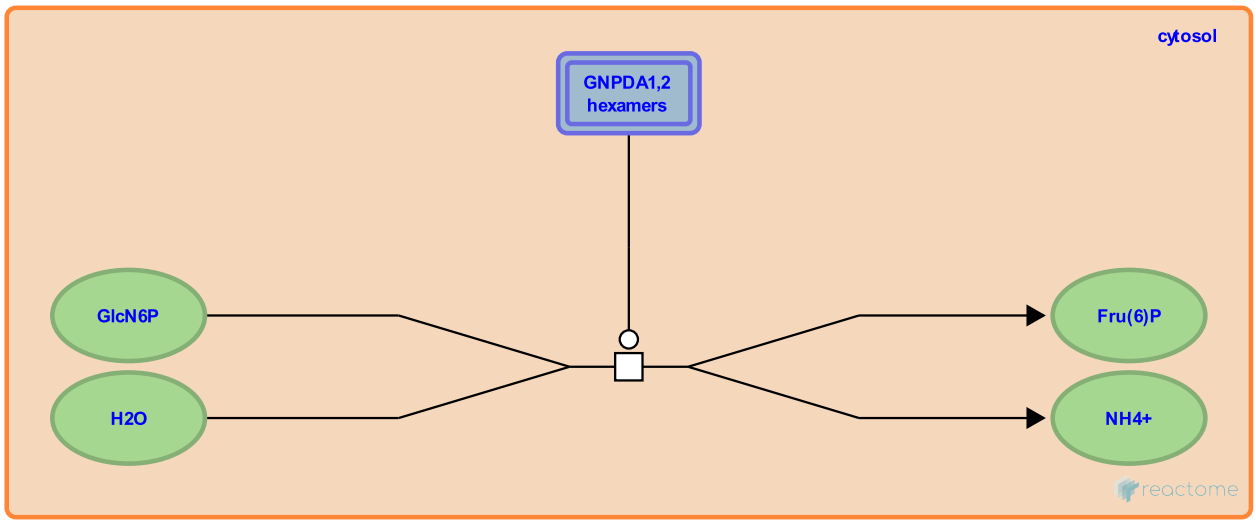
GNPDA1,2 hexamers deaminate GlcN6P to Fru(6)P ↗

Location: Glycolysis

Stable identifier: R-HSA-6799604

Type: transition

Compartments: cytosol



Glucosamine-6-phosphate isomerases 1 and 2 (GNPDA1, 2) catalyse the reversible deamination and with an aldo/keto isomerisation of D-glucosamine 6-phosphate (GlcN6P) to D-fructose 6-phosphate (Fru(6)P) and ammonia (NH3). GNDPA1 and 2 function as homohexamers in the cytosol. This reaction could provide a source of energy from catabolic pathways of hexosamines found in glycoproteins and glycolipids (Wolosker et al. 1998, Zhang et al. 2003, Arreola et al. 2003).

Followed by: D-fructose 6-phosphate + ATP => D-fructose 1,6-bisphosphate + ADP

Literature references

Chen, G., Wan, T., Li, N., Zou, D., Cao, X., Zhang, W. et al. (2003). Cloning and functional characterization of GNPI2, a novel human homolog of glucosamine-6-phosphate isomerase/oscillin. *J. Cell. Biochem., 88*, 932-40. ↗

Schnaar, RL., Wolosker, H., Kline, D., Cameron, AM., Snyder, SH., Blackshaw, S. et al. (1998). Molecularly cloned mammalian glucosamine-6-phosphate deaminase localizes to transporting epithelium and lacks oscillin activity. *FASEB J., 12*, 91-9. ↗

Horjales, E., Arreola, R., Morante, ML., Valderrama, B. (2003). Two mammalian glucosamine-6-phosphate deaminases: a structural and genetic study. *FEBS Lett., 551*, 63-70. ↗

Editions

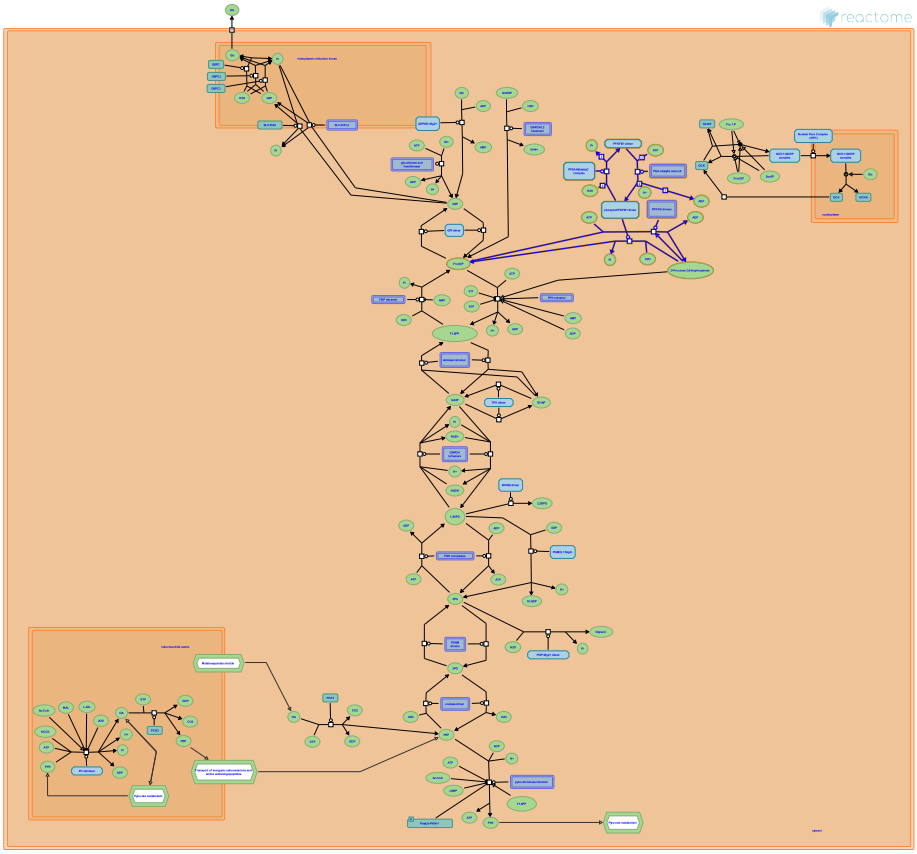
2015-09-25	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

Regulation of glycolysis by fructose 2,6-bisphosphate metabolism ↗

Location: Glycolysis

Stable identifier: R-HSA-9634600

Compartments: cytosol



The committed step of glycolysis is the phosphorylation of D-fructose 6-phosphate (Fru(6)P) to form D-fructose 1,6-bisphosphate, catalyzed by phosphofructokinase 1 (PFK) tetramer. PFK can be allosterically activated by D-fructose 2,6-bisphosphate whose levels are increased in response to insulin signaling and decreased in response to glucagon signaling, through the reactions annotated here (Pilkis et al. 1995).

Literature references

Kurland, IJ., Lange, AJ., Pilkis, SJ., Claus, TH. (1995). 6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase: a metabolic signaling enzyme. *Annu Rev Biochem, 64*, 799-835. ↗

Editions

2008-09-10	Reviewed	Harris, RA.
2019-01-12	Edited	D'Eustachio, P.

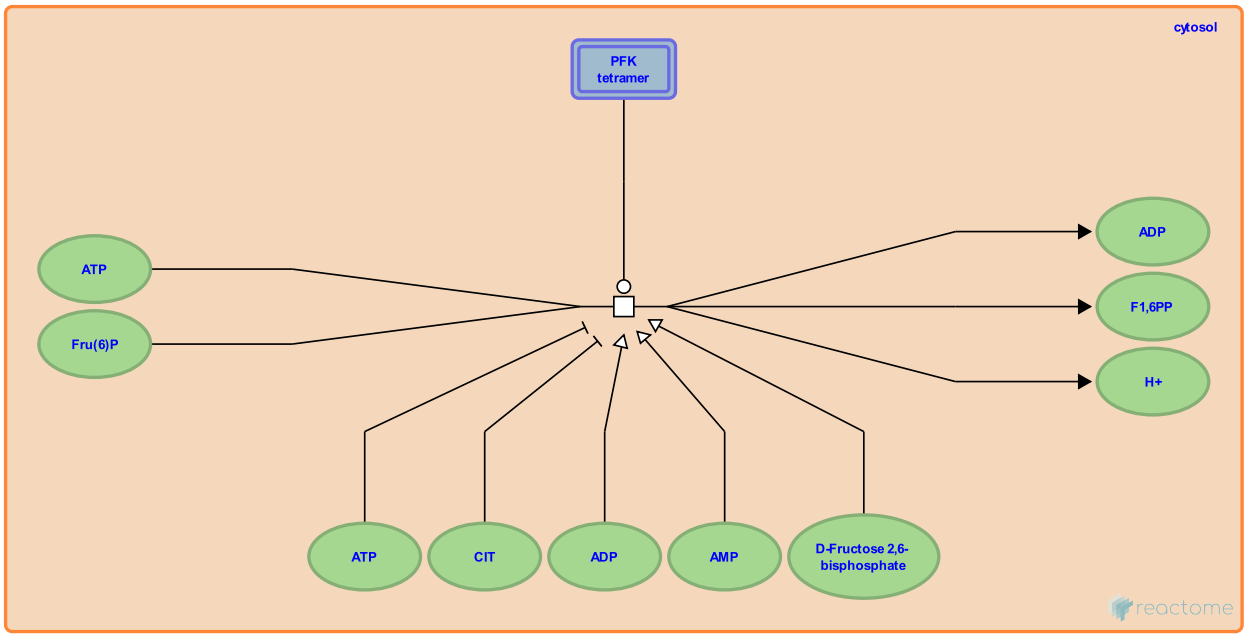
D-fructose 6-phosphate + ATP => D-fructose 1,6-bisphosphate + ADP ↗

Location: Glycolysis

Stable identifier: R-HSA-70467

Type: transition

Compartments: cytosol



Cytosolic phosphofructokinase 1 catalyzes the reaction of fructose 6-phosphate and ATP to form fructose 1,6-bisphosphate and ADP. This reaction, irreversible under physiological conditions, is the rate limiting step of glycolysis. Phosphofructokinase 1 activity is allosterically regulated by ATP, citrate, and fructose 2,6-bisphosphate.

Phosphofructokinase 1 is active as a tetramer (although higher order multimers, not annotated here, may form in vivo). Two isoforms of phosphofructokinase 1 monomer, L and M, are widely expressed in human tissues. Different tissues can contain different homotetramers or heterotetramers: L4 in liver, M4 in muscle, and all possible heterotetramers, L4, L3M, L2M2, LM3, and M4, in red blood cells, for example (Raben et al. 1995; Vora et al. 1980, 1987; Vora 1981). A third isoform, P, is abundant in platelets, where it is found in P4, P3L, P2L2, and PL3 tetramers (Eto et al. 1994; Vora et al. 1987).

Preceded by: alpha-D-glucose 6-phosphate <=> D-fructose 6-phosphate, GNPDA1,2 hexamers deaminate GlcN6P to Fru(6)P

Followed by: D-fructose 1,6-bisphosphate <=> dihydroxyacetone phosphate + D-glyceraldehyde 3-phosphate

Literature references

Vora, S. (1981). Isozymes of human phosphofructokinase in blood cells and cultured cell lines: molecular and genetic evidence for a trigenic system. *Blood, 57*, 724-32. ↗

Piomelli, S., Vora, S., Seaman, C., Durham, S. (1980). Isozymes of human phosphofructokinase: identification and subunit structural characterization of a new system. *Proc Natl Acad Sci U S A, 77*, 62-6. ↗

Sherman, JB., Raben, N., Spiegel, R., Heinisch, J., Nakajima, H., Plotz, P. et al. (1995). Functional expression of human mutant phosphofructokinase in yeast: genetic defects in French Canadian and Swiss patients with phosphofructokinase deficiency. *Am J Hum Genet, 56*, 131-41. ↗

Yazaki, Y., Kadowaki, T., Moriuchi, R., Nagataki, S., Hayakawa, T., Kawasaki, E. et al. (1994). Cloning of a complete protein-coding sequence of human platelet-type phosphofructokinase isozyme from pancreatic islet. *Biochem Biophys Res Commun, 198*, 990-8. ↗

Danon, MJ., Spear, D., Harker, D., Vora, S., DiMauro, S. (1987). Characterization of the enzymatic defect in late-onset muscle phosphofructokinase deficiency. New subtype of glycogen storage disease type VII. *J Clin Invest, 80*, 1479-85. ↗

Editions

2009-12-17	Revised	D'Eustachio, P.

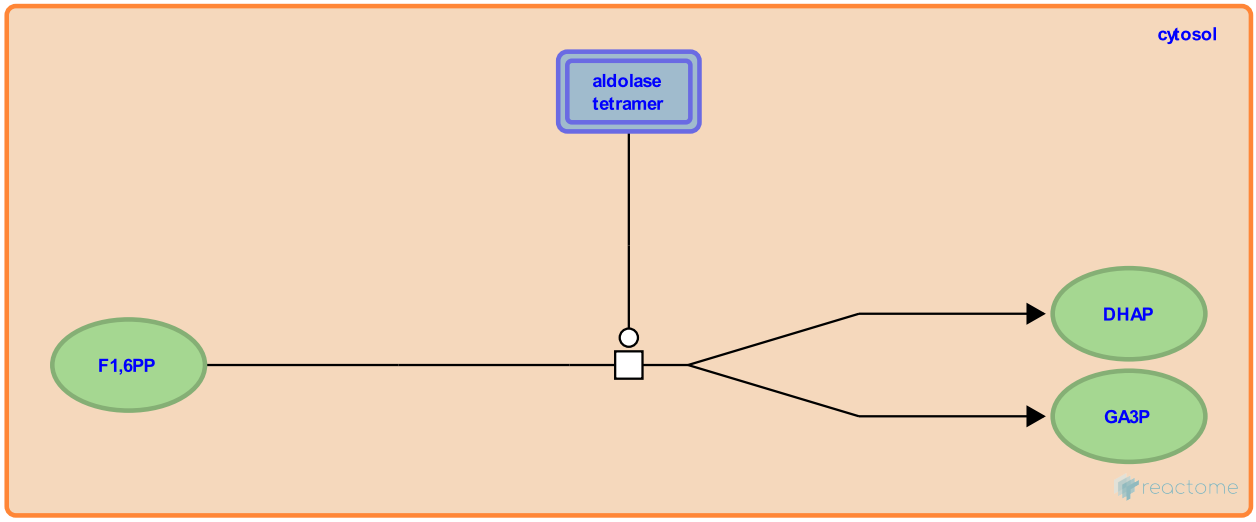
D-fructose 1,6-bisphosphate <=> dihydroxyacetone phosphate + D-glyceraldehyde 3-phosphate ↗

Location: Glycolysis

Stable identifier: R-HSA-71496

Type: transition

Compartments: cytosol



Cytosolic aldolase catalyzes the cleavage of D-fructose 1,6-bisphosphate to yield dihydroxyacetone phosphate and D-glyceraldehyde 3-phosphate. The active form of aldolase 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; Freemont et al. 1984, 1988).

Preceded by: D-fructose 6-phosphate + ATP => D-fructose 1,6-bisphosphate + ADP

Followed by: dihydroxyacetone phosphate <=> D-glyceraldehyde 3-phosphate

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., Freemont, PS., Fothergill, LA. (1984). Human skeletal-muscle aldolase: N-terminal sequence analysis of CNBr- and o-iodosobenzoic acid-cleavage fragments. *Arch Biochem Biophys, 228*, 342-52. ↗

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

Editions

2009-12-17	Revised	D'Eustachio, P.

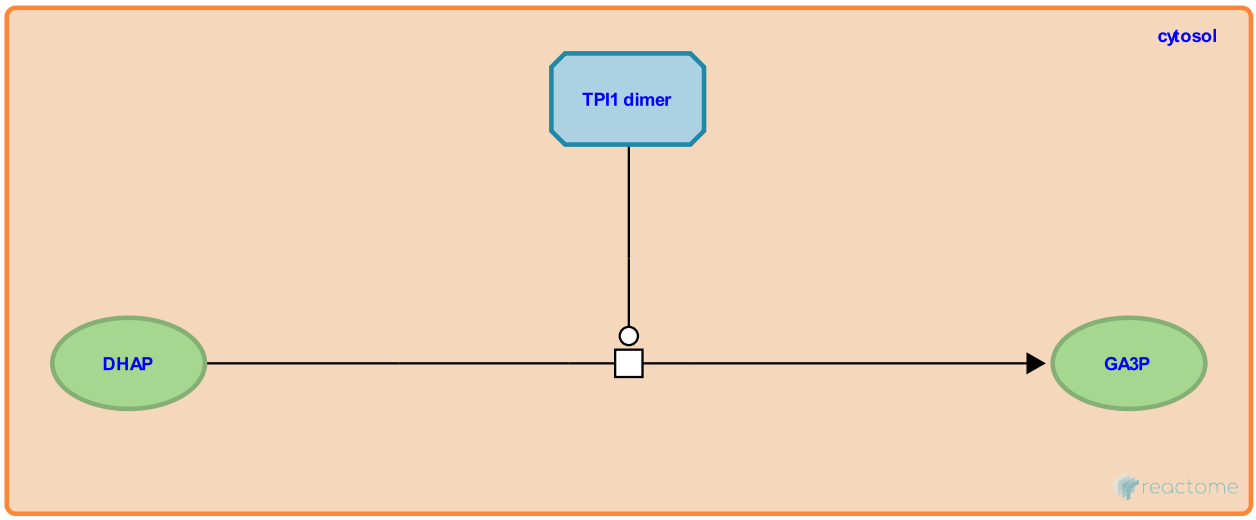
dihydroxyacetone phosphate <=> D-glyceraldehyde 3-phosphate ↗

Location: Glycolysis

Stable identifier: R-HSA-70454

Type: transition

Compartments: cytosol



Cytosolic triose phosphate isomerase catalyzes the freely reversible interconversion of dihydroxyacetone phosphate and glyceraldehyde 3-phosphate (Lu et al. 1984). The active form of the enzyme is a homodimer (Kinoshita et al. 2005).

Preceded by: D-fructose 1,6-bisphosphate <=> dihydroxyacetone phosphate + D-glyceraldehyde 3-phosphate

Followed by: D-glyceraldehyde 3-phosphate + orthophosphate + NAD+ <=> 1,3-bisphospho-D-glycerate + NADH + H+

Literature references

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

Maruki, R., Warizaya, M., Nishimura, S., Kinoshita, T., Nakajima, H. (2005). Structure of a high-resolution crystal form of human triosephosphate isomerase: improvement of crystals using the gel-tube method. *Acta Crystallogr Sect F Struct Biol Cryst Commun, 61*, 346-9. ↗

Editions

2009-12-17	Revised	D'Eustachio, P.

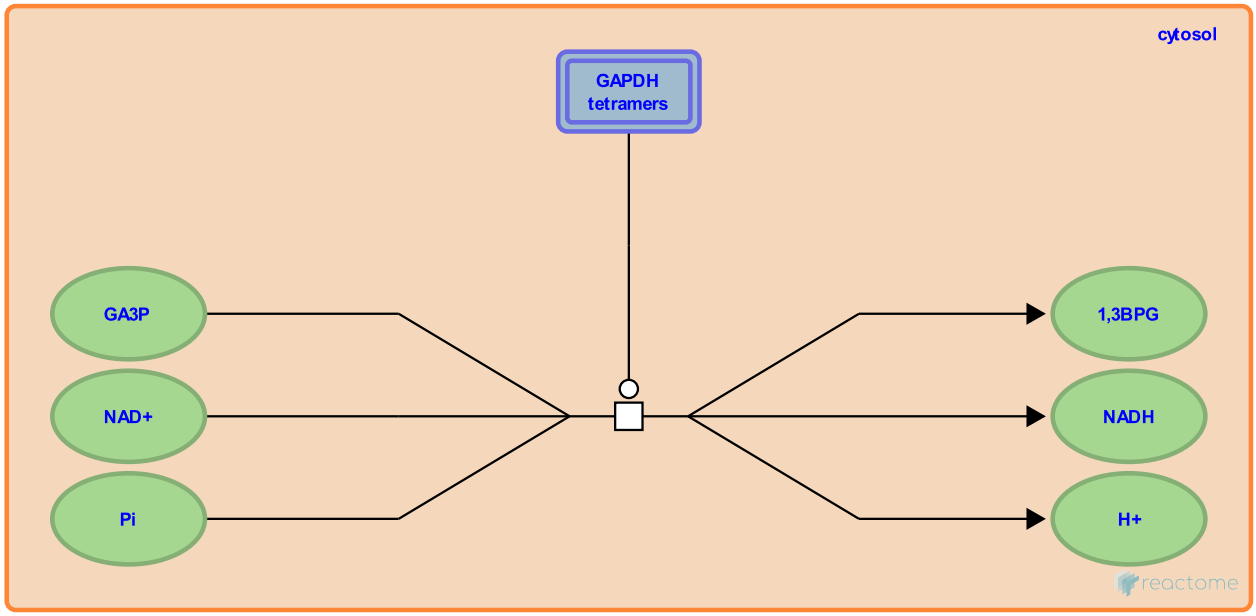
D-glyceraldehyde 3-phosphate + orthophosphate + NAD+ <=> 1,3-bisphospho-D-glycerate + NADH + H+ ↗

Location: Glycolysis

Stable identifier: R-HSA-70449

Type: transition

Compartments: cytosol



Cytosolic glyceraldehyde 3-phosphate dehydrogenase catalyzes the reversible reaction of glyceraldehyde 3-phosphate, orthophosphate, and NAD+ to form NADH + H+ and 1,3-bisphosphoglycerate, the first energy rich intermediate of glycolysis. The biochemical details of this reaction were worked out by C and G Cori and their colleagues (Taylor et al. 1948; Cori et al. 1948).

While there are multiple human glyceraldehyde 3-phosphate dehydrogenase-like pseudogenes, there is only one glyceraldehyde 3-phosphate dehydrogenase gene expressed in somatic tissue (Benham and Povey 1989; Heinz and Freimuller 1982; Ercolani et al. 1988), and studies of aged human erythrocytes suggest 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 glyceraldehyde 3-phosphate dehydrogenase whose expression is confined to spermatogenic cells of the testis (Welch et al. 2000).

Preceded by: dihydroxyacetone phosphate <=> D-glyceraldehyde 3-phosphate

Followed by: BPGM dimer isomerises 1,3BPG to 2,3BPG, 1,3-bisphospho-D-glycerate + ADP <=> 3-phospho-D-glycerate + ATP

Literature references

Benham, FJ., Povey, S. (1989). Members of the human glyceraldehyde-3-phosphate dehydrogenase-related gene family map to dispersed chromosomal locations. *Genomics, 5*, 209-14. ↗

VELICK, SF., TAYLOR, JF. (1948). The prosthetic group of crystalline d-glyceraldehyde-3-phosphate dehydrogenase. *J. Biol. Chem., 173*, 619-26. ↗

Cori, CF., Slein, MW., Cori, GT. (1948). Crystalline D-glyceraldehyde-3-phosphate dehydrogenase from rabbit muscle . *J Biol Chem, 173*, 605-618. ↗

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. ↗

Editions

2009-12-17	Revised	D'Eustachio, P.

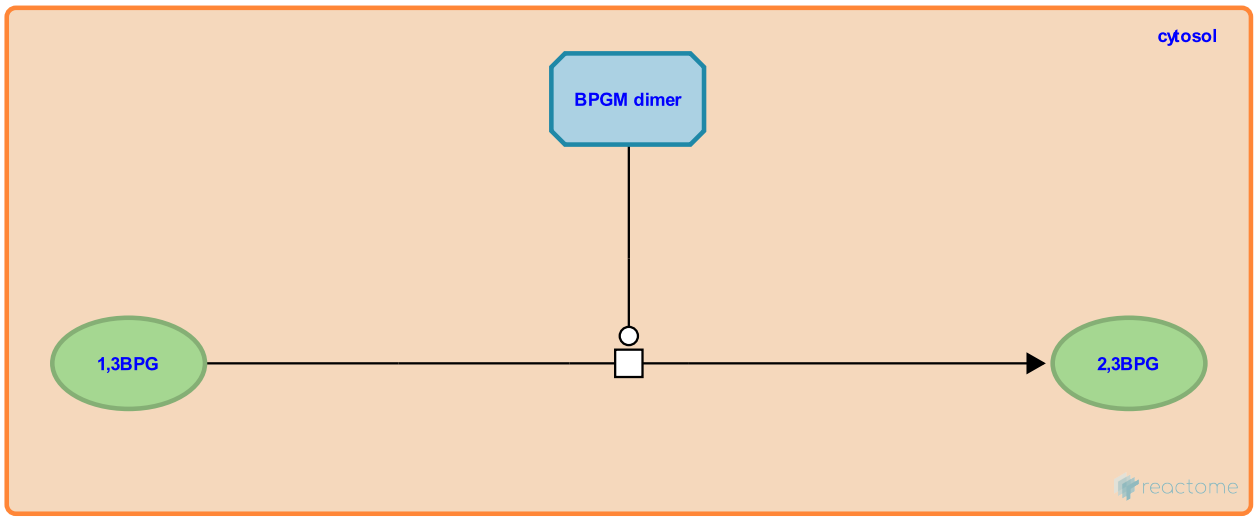
BPGM dimer isomerises 1,3BPG to 2,3BPG ↗

Location: Glycolysis

Stable identifier: R-HSA-6798335

Type: transition

Compartments: cytosol



Bisphosphoglycerate mutase (BPGM) is an erythrocyte-specific trifunctional enzyme. One of its functions is the isomerisation of 1,3-bisphosphoglycerate (1,3BPG) to 2,3-bisphosphoglycerate (2,3BPG) (Rose 1968). In red blood cells, 2,3BPG is the main allosteric effector of hemoglobin, binding preferentially to the deoxygenated hemoglobin tetramer, thus reducing oxygen affinity (Arnone 1972).

Preceded by: D-glyceraldehyde 3-phosphate + orthophosphate + NAD+ <=> 1,3-bisphospho-D-glycerate + NADH + H+

Literature references

Rose, ZB. (1968). The purification and properties of diphosphoglycerate mutase from human erythrocytes. *J. Biol. Chem., 243*, 4810-20. ↗

Arnone, A. (1972). X-ray diffraction study of binding of 2,3-diphosphoglycerate to human deoxyhaemoglobin. *Nature, 237*, 146-9. ↗

Editions

2015-09-18	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

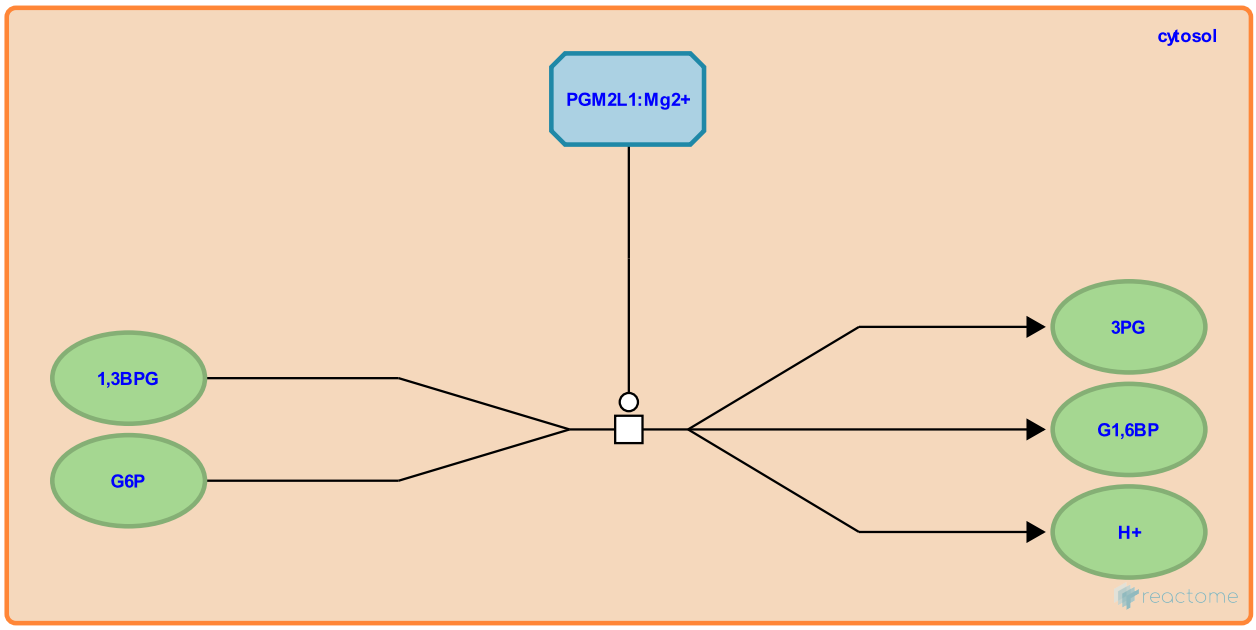
PGM2L1:Mg2+ phosphorylates G6P to G1,6BP ↗

Location: Glycolysis

Stable identifier: R-HSA-8955760

Type: transition

Compartments: cytosol



1,3-bisphosphoglycerate (1,3BPG) is the first energy rich intermediate of glycolysis. Cytosolic glucose 1,6-bisphosphate synthase (PGM2L1) utilises 1,3BPG as a phosphate donor to phosphorylate a series of 1-phosphate sugars. Although 5- and 6-phosphate sugars are poor substrates for PGM2L1, glucose 6-phosphate (G6P) is the exception (Maliekal et al. 2007, Veiga-da-Cunha et al. 2008). PGM2L1 complexed with Mg2+ as cofactor, phosphorylates G6P to glucose 1,6-bisphosphate (G1,6BP), a cofactor for phosphomutases and a putative regulator of glycolysis. PGM2L1 is mainly expressed in brain where its activity is particularly high (Maliekal et al. 2007).

Preceded by: HK1,2,3,GCK,HKDC1 phosphorylate Glc to form G6P

Followed by: PGP:Mg2+ dimer hydrolyses 3PG to glycerol, 3-Phospho-D-glycerate <=> 2-Phospho-D-glycerate

Literature references

Maliekal, P., Matthijs, G., Vleugels, W., Veiga-da-Cunha, M., Van Schaftingen, E. (2008). Mammalian phosphomannomutase PMM1 is the brain IMP-sensitive glucose-1,6-bisphosphatase. *J. Biol. Chem., 283*, 33988-93. ↗

Maliekal, P., Veiga-da-Cunha, M., Sokolova, T., Van Schaftingen, E., Vertommen, D. (2007). Molecular identification of mammalian phosphopentomutase and glucose-1,6-bisphosphate synthase, two members of the alpha-D-phosphohexomutase family. *J Biol Chem, 282*, 31844-51. ↗

Editions

2017-01-13	Authored, Edited	Jassal, B.
2017-01-30	Reviewed	D'Eustachio, P.

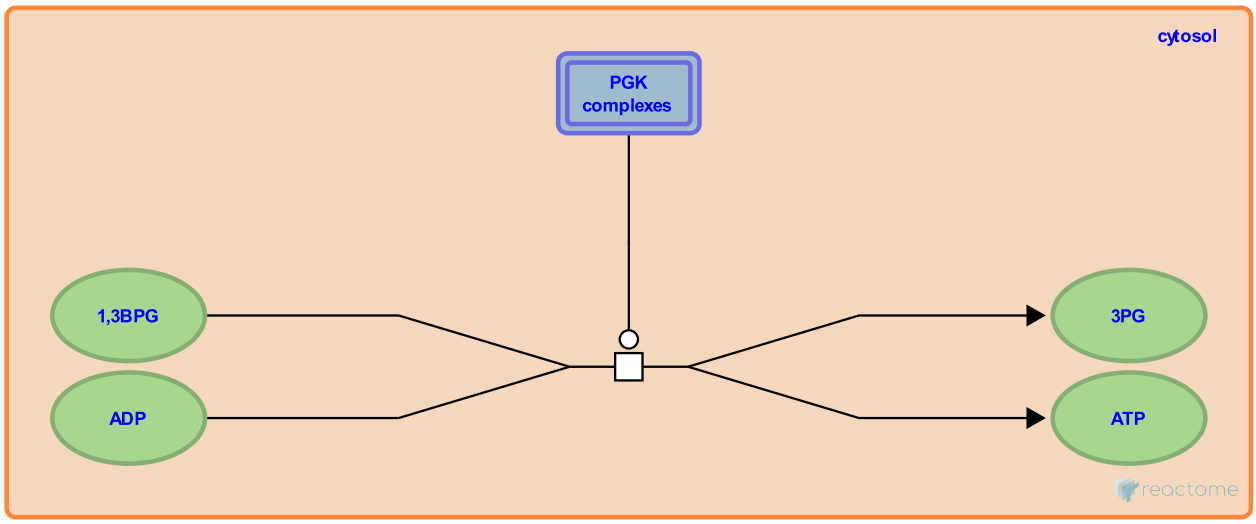
1,3-bisphospho-D-glycerate + ADP <=> 3-phospho-D-glycerate + ATP ↗

Location: Glycolysis

Stable identifier: R-HSA-71850

Type: transition

Compartments: cytosol



Cytosolic phosphoglycerate kinase (PGK) catalyzes the reaction of ADP and 1,3-bisphosphoglycerate (1,3BPG) to form D glyceraldehyde 3-phosphate (3PG) and ATP. The active form of the enzyme is a monomer and requires Mg++ (Yoshida and Watanabe 1972; Huang et al. 1980a,b). This is the first substrate level phosphorylation reaction in glycolysis. Two PGK isoforms are known: PGK1 is widely expressed in the body while PGK2 (Chen et al. 1976; McCarrey & Thomas 1987) appears to be confined to sperm cells.

Preceded by: D-glyceraldehyde 3-phosphate + orthophosphate + NAD+ <=> 1,3-bisphospho-D-glycerate + NADH + H+

Followed by: PGP:Mg2+ dimer hydrolyses 3PG to glycerol, 3-Phospho-D-glycerate <=> 2-Phospho-D-glycerate

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. ↗

Thomas, K., McCarrey, JR. (1987). Human testis-specific PGK gene lacks introns and possesses characteristics of a processed gene. *Nature, 326*, 501-5. ↗

Editions

2009-12-17	Revised	D'Eustachio, P.
2015-11-09	Revised	D'Eustachio, P.
2015-11-09	Reviewed	Jassal, B.

PGP:Mg2+ dimer hydrolyses 3PG to glycerol ↗

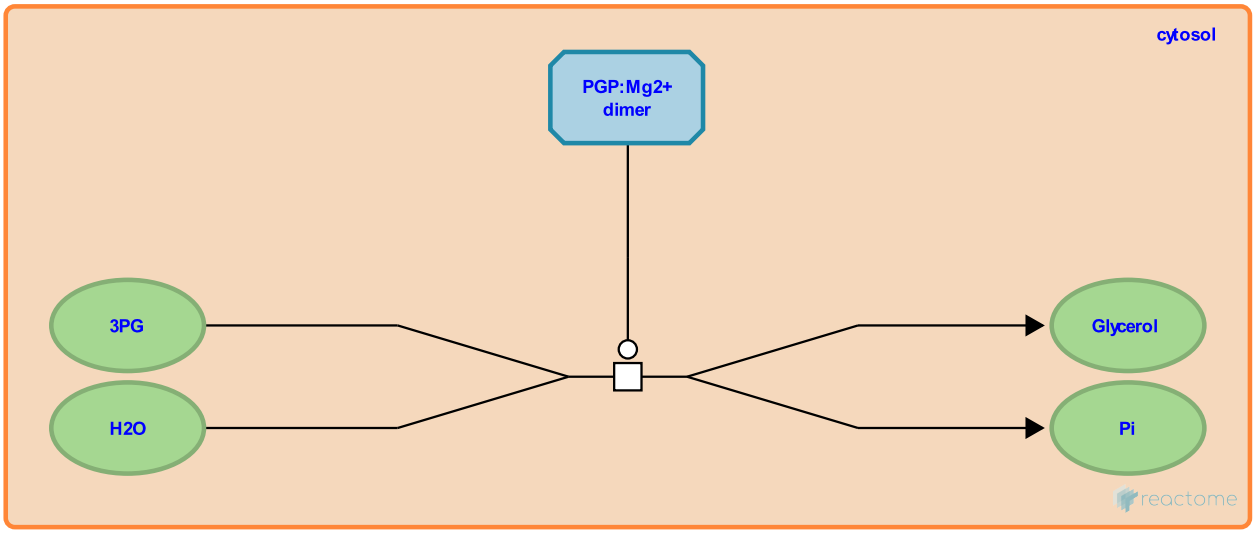
Location: Glycolysis

Stable identifier: R-HSA-8955794

Type: transition

Compartments: cytosol

Inferred from: Pgp:Mg2+ dimer hydrolyses 3PG to glycerol (Rattus norvegicus)



Glycerol-3-phosphate (aka 3-phospho-D-glycerate, 3PG) is a metabolic intermediate of glucose, lipid and energy metabolism. Its cellular levels may be regulated by cytosolic glycerol-3-phosphate phosphatase (PGP aka G3PP), which hydrolyses 3PG to glycerol. PGP functions as a homodimer, binding one Mg2+ ion per subunit. The function of the human protein is inferred from rat Pgp characterisation and functional studies (Mugabo et al. 2016).

Preceded by: 1,3-bisphospho-D-glycerate + ADP <=> 3-phospho-D-glycerate + ATP, PGM2L1:Mg2+ phosphorylates G6P to G1,6BP

Literature references

Gezzar, S., Zhang, D., Lamontagne, J., Al-Mass, A., Zhao, S., Iglesias, J. et al. (2016). Identification of a mammalian glycerol-3-phosphate phosphatase: Role in metabolism and signaling in pancreatic β-cells and hepatocytes. *Proc. Natl. Acad. Sci. U.S.A., 113*, E430-9. ↗

Editions

2017-01-13	Authored, Edited	Jassal, B.
2017-01-30	Reviewed	D'Eustachio, P.

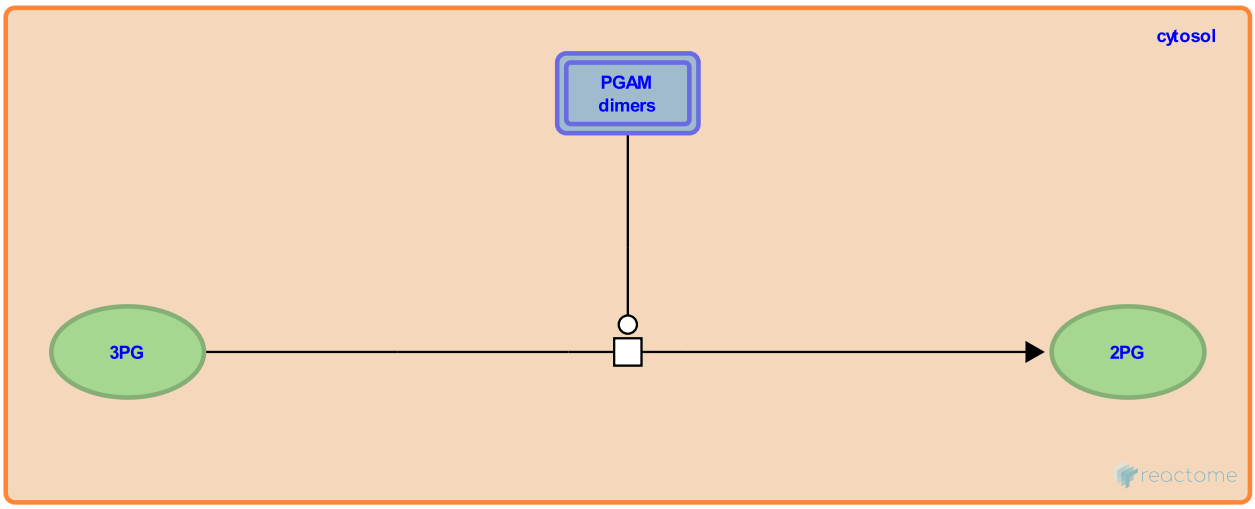
3-Phospho-D-glycerate <=> 2-Phospho-D-glycerate ↗

Location: Glycolysis

Stable identifier: R-HSA-71654

Type: transition

Compartments: cytosol



Cytosolic phosphoglycerate mutase catalyzes the reversible isomerisation of 3- and 2-phosphoglycerate. The active form of the enzyme is a dimer. There are two isoforms of this enzyme, PGAM1 (isoform B, widely expressed in non-muscle tissue) and PGAM2 (isoform M, expressed in muscle) (Blouquit et al. 1988; Omenn and Cheung 1974; Repiso et al. 2005; Tsujino et al. 1993).

Preceded by: 1,3-bisphospho-D-glycerate + ADP <=> 3-phospho-D-glycerate + ATP, PGM2L1:Mg2+ phosphorylates G6P to G1,6BP

Followed by: 2-Phospho-D-glycerate <=> Phosphoenolpyruvate + H2O

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. ↗

Calvin, MC., Prome, JC., Rosa, R., Cohen-Solal, M., Prome, D., Blouquit, Y. et al. (1988). Sequence of the human erythrocyte phosphoglycerate mutase by microsequencer and mass spectrometry. *J Biol Chem, 263*, 16906-10. ↗

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

2009-12-17	Revised	D'Eustachio, P.

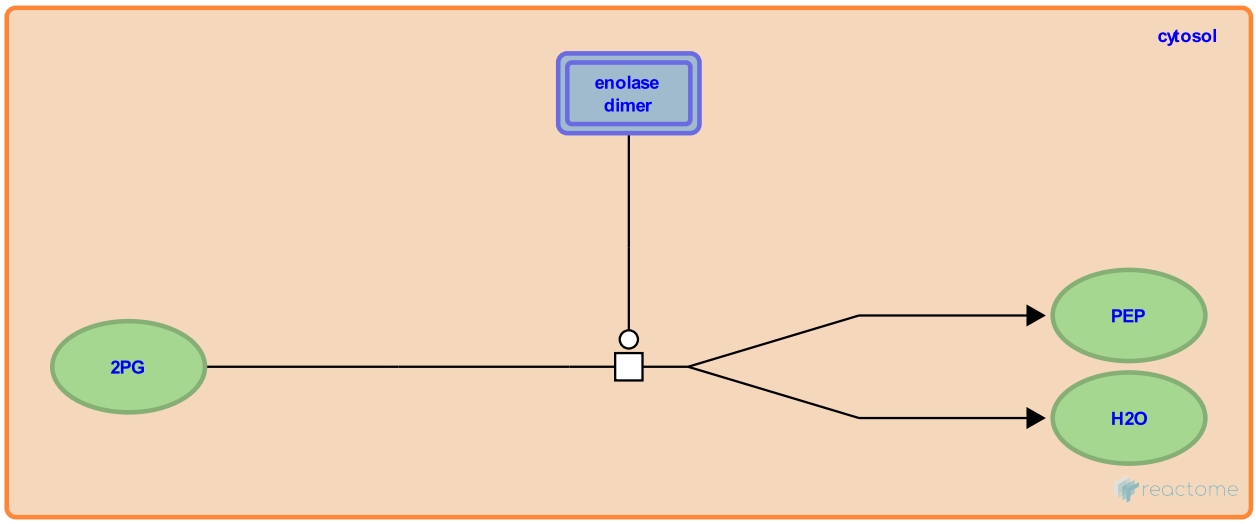
2-Phospho-D-glycerate <=> Phosphoenolpyruvate + H2O ↗

Location: Glycolysis

Stable identifier: R-HSA-71660

Type: transition

Compartments: cytosol



Cytosolic enolase catalyzes the reversible reaction of 2 phosphoglycerate to form phosphoenolpyruvate and water, elevating the transfer potential of the phosphoryl group.

Enolase is a homodimer and requires Mg++ for activity. Three isozymes have been purified and biochemically characterized. The alpha isoform is expressed in many normal human tissues (Giallongo et al. 1986). The beta isoform 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 is normally expressed in neural tissue and is of possible clinical interest as a marker of some types of neuroendocrine and lung tumors (McAleese et al. 1988). Biochemical studies of the homologous rat proteins indicate that both homo- and heterodimers of enolase form and are enzymatically active (Rider and Taylor 1974).

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: 3-Phospho-D-glycerate <=> 2-Phospho-D-glycerate

Followed by: PKM dephosphorylates PEP to PYR

Literature references

Rider, CC., Taylor, CB. (1974). Enolase isoenzymes in rat tissues. Electrophoretic, chromatographic, immunological and kinetic properties. *Biochim Biophys Acta, 365*, 285-300. ↗

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. ↗

Stapel, SO., de Jong, WW., Williams, LA., Lietman, T., Wistow, GJ., Piatigorsky, J. et al. (1988). Tau-crystallin/alpha-enolase: one gene encodes both an enzyme and a lens structural protein. *J Cell Biol, 107*, 2729-36. ↗

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. ↗

Eddy, EM., Willis, WD., Dai, Q., Nakamura, N., Brown, PR., Goulding, EH. et al. (2013). Disruption of a spermatogenic cell-specific mouse enolase 4 (eno4) gene causes sperm structural defects and male infertility. *Biol Reprod, 88*, 90. ↗

Editions

2004-09-21	Authored	D'Eustachio, P.
2009-12-17	Revised	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

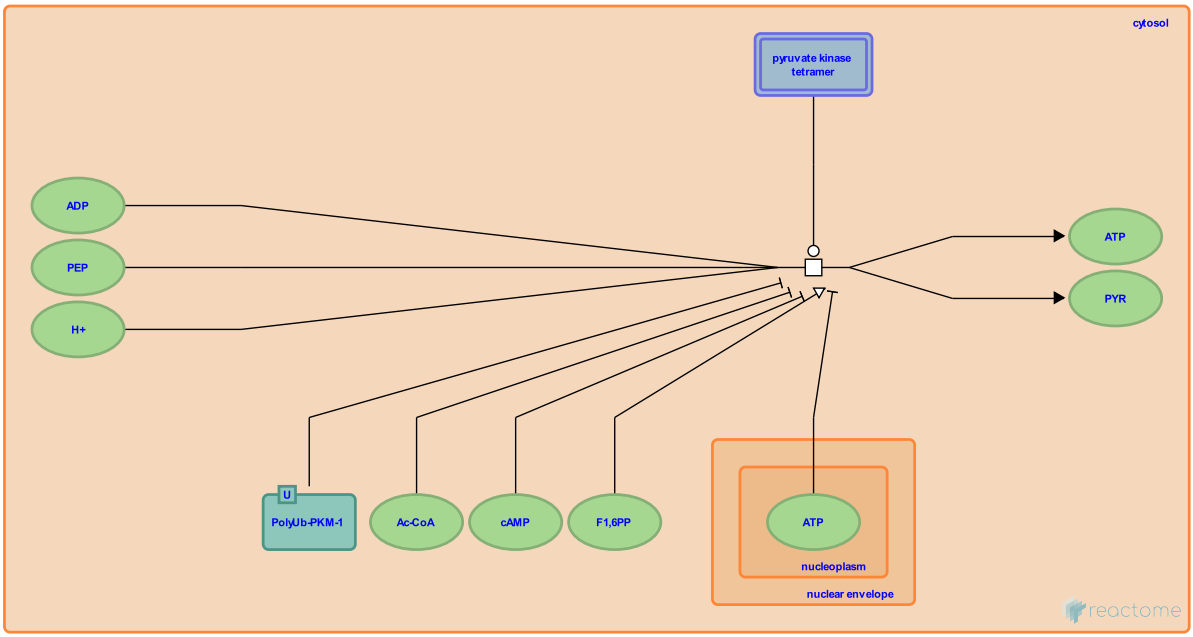
PKM dephosphorylates PEP to PYR ↗

Location: Glycolysis

Stable identifier: R-HSA-71670

Type: transition

Compartments: cytosol



Cytosolic pyruvate kinase catalyzes the transfer of a high-energy phosphate from phosphoenolpyruvate to ADP, forming pyruvate and ATP. This reaction, an instance of substrate-level phosphorylation, is essentially irreversible under physiological conditions.

Four isozymes of human pyruvate kinase have been described, L, R, M1 and M2. Isozymes L and R are encoded by alternatively spliced transcripts of the PKLR gene; isozymes M1 and M2 are encoded by alternatively spliced transcripts of PKM2. In the body, L pyruvate kinase is found in liver (Tani et al. 1988), R in red blood cells (Kanno et al. 1991), M1 in muscle, heart and brain (Takenaka et al. 1991), and M2 in early fetal tissues and tumors (e.g., Lee et al. 2008). In all cases, the active form of the enzyme is a homotetramer, activated by fructose 1,6-bisphosphate (Valentini et al. 2002; Dombrauckas et al. 2005). Mutations in PKLR have been associated with hemolytic anemias (e.g., Zanella et al. 2005).

Preceded by: 2-Phospho-D-glycerate <=> Phosphoenolpyruvate + H2O

Literature references

Miwa, S., Fujii, H., Kanno, H., Hirono, A. (1991). cDNA cloning of human R-type pyruvate kinase and identification of a single amino acid substitution (Thr384----Met) affecting enzymatic stability in a pyruvate kinase variant (PK Tokyo) associated with hereditary hemolytic anemia. *Proc Natl Acad Sci U S A, 88*, 8218-21. ↗

Matsuda, T., Noguchi, T., Hirai, H., Takenaka, M., Imai, E., Yamada, K. et al. (1991). Isolation and characterization of the human pyruvate kinase M gene. *Eur J Biochem, 198*, 101-6. ↗

Schild-Poulter, C., Kuljanin, M., Lajoie, GA., Maitland, MER., Wang, X. (2021). Proteomic analysis of ubiquitination substrates reveals a CTLH E3 ligase complex-dependent regulation of glycolysis. *FASEB J, 35*, e21825. ↗

Miwa, S., Nagata, S., Fujii, H., Tani, K. (1988). Human liver type pyruvate kinase: complete amino acid sequence and the expression in mammalian cells. *Proc Natl Acad Sci U S A, 85*, 1792-5. ↗

Kim, J., Han, YM., Lee, J., Kim, HK. (2008). Pyruvate kinase isozyme type M2 (PKM2) interacts and cooperates with Oct-4 in regulating transcription. *Int J Biochem Cell Biol, 40*, 1043-54. ↗

Editions

2004-09-21	Authored	D'Eustachio, P.
2009-12-17	Revised	D'Eustachio, P.
2024-02-23	Reviewed	Hill, DP.

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