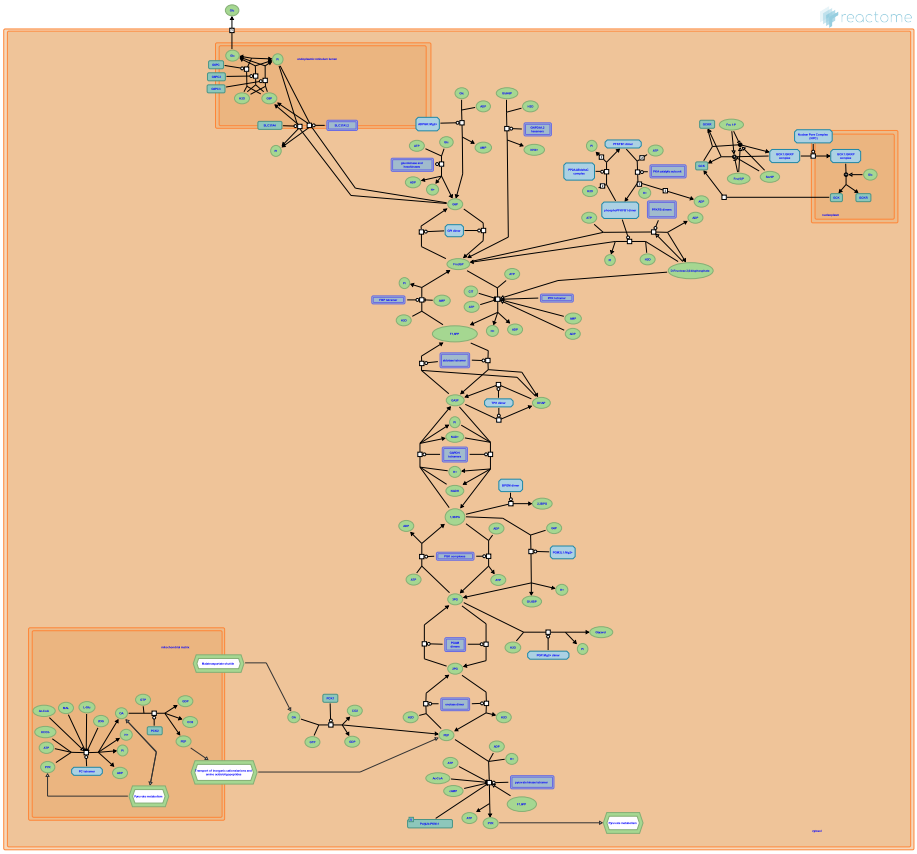
Glucose metabolism



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

10/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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

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

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

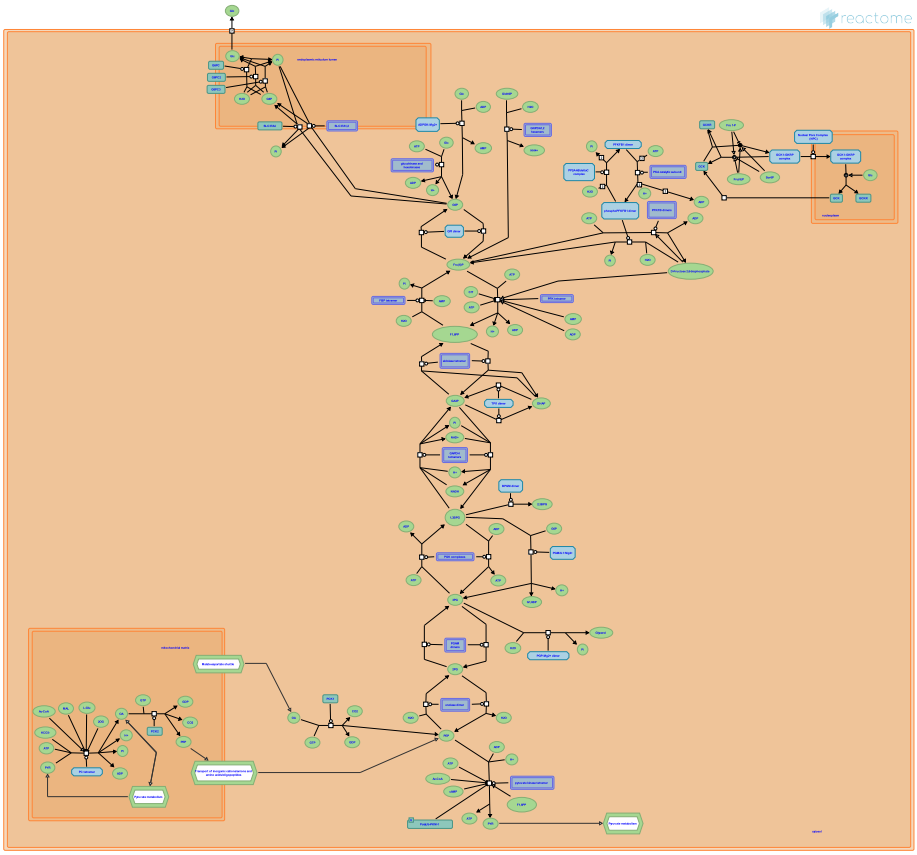
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Glucose metabolism ↗

Stable identifier: R-HSA-70326



Glucose is the major form in which dietary sugars are made available to cells of the human body. Its breakdown is a major source of energy for all cells, and is essential for the brain and red blood cells. Glucose utilization begins with its uptake by cells and conversion to glucose 6-phosphate, which cannot traverse the cell membrane. Fates open to cytosolic glucose 6-phosphate include glycolysis to yield pyruvate, glycogen synthesis, and the pentose phosphate pathway. In some tissues, notably the liver and kidney, glucose 6-phosphate can be synthesized from pyruvate by the pathway of gluconeogenesis.

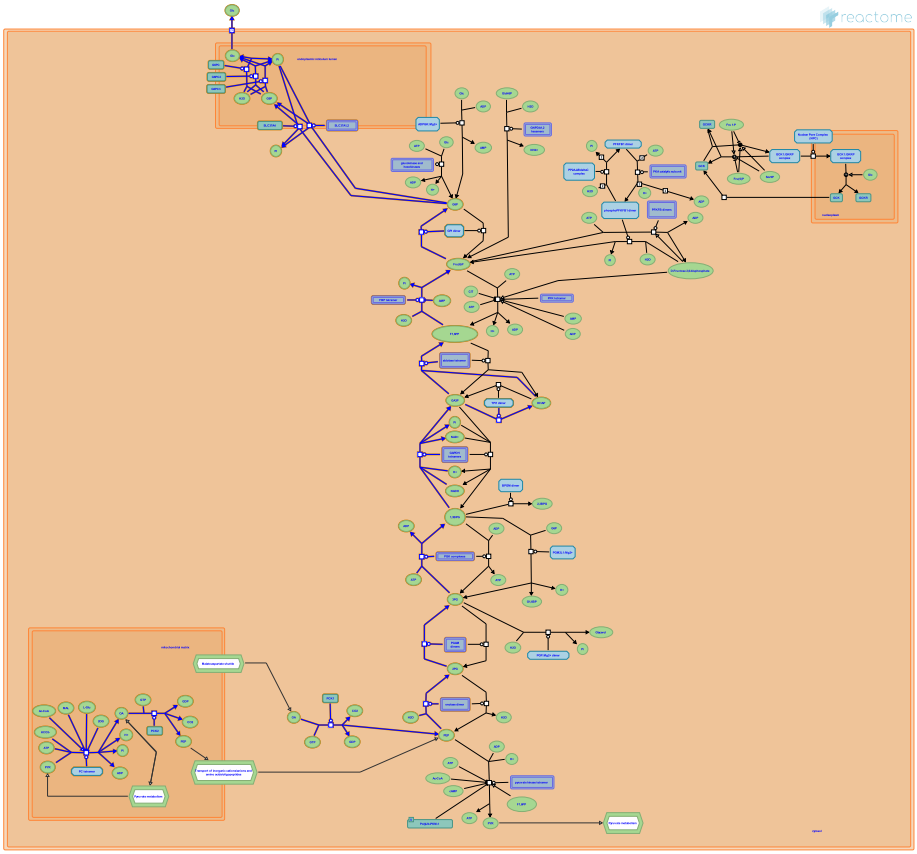
Editions

2003-02-05	Authored	Schmidt, EE.
2009-12-12	Revised	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

Gluconeogenesis ↗

Location: Glucose metabolism

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

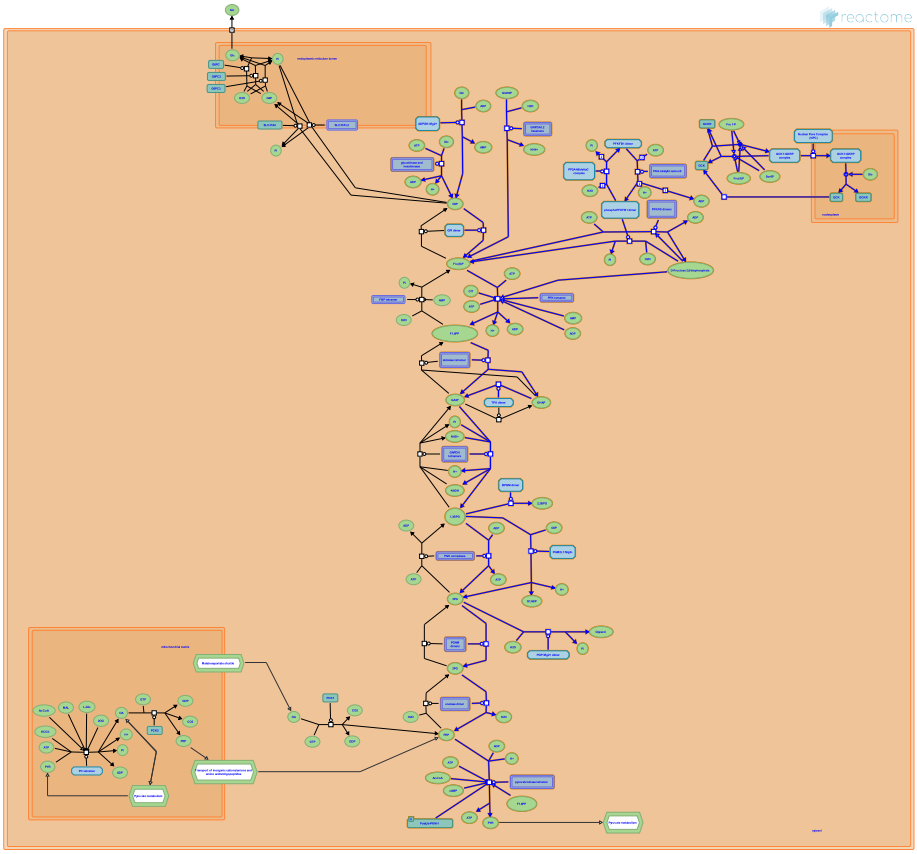
2008-09-10	Reviewed	Harris, RA.
2008-09-13	Revised	D'Eustachio, P.
2022-08-29	Revised	D'Eustachio, P.
2022-08-29	Reviewed	Hill, DP.
2024-03-06	Edited	D'Eustachio, P.

Glycolysis ↗

Location: Glucose metabolism

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.

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