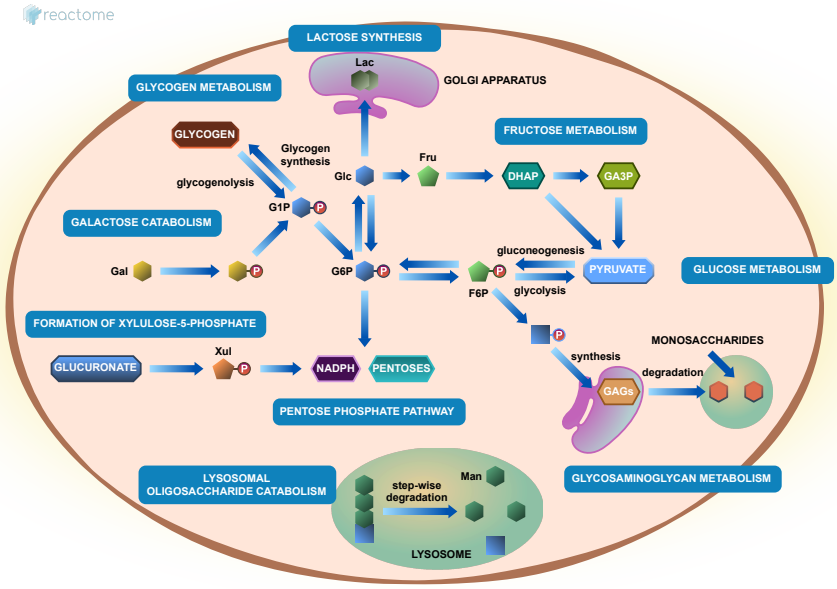
Metabolism of carbohydrates



Cameselle, JC., D'Eustachio, P., Jassal, B., Matsui, T., Ribeiro, JM., Schmidt, EE.

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

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.

26/04/2024

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. ↗

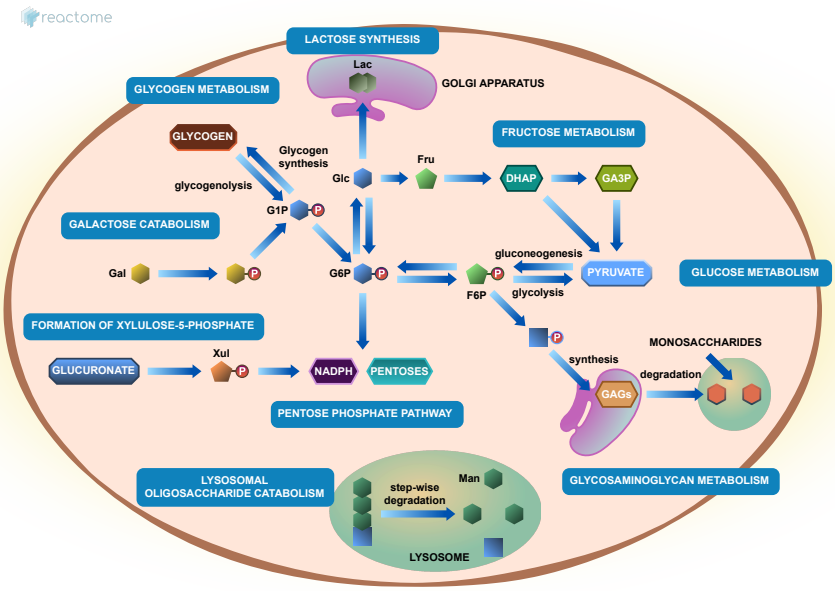
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 11 pathways (see Table of Contents)

Metabolism of carbohydrates ↗

Stable identifier: R-HSA-71387



Starches and sugars are major constituents of the human diet and the catabolism of monosaccharides, notably glucose, derived from them is an essential part of human energy metabolism (Dashty 2013). Glucose can be catabolized to pyruvate (glycolysis) and pyruvate synthesized from diverse sources can be metabolized to form glucose (gluconeogenesis). Glucose can be polymerized to form glycogen under conditions of glucose excess (glycogen synthesis), and glycogen can be broken down to glucose in response to stress or starvation (glycogenolysis). Other monosaccharides prominent in the diet, fructose and galactose, can be converted to glucose. The disaccharide lactose, the major carbohydrate in breast milk, is synthesized in the lactating mammary gland. The pentose phosphate pathway allows the synthesis of diverse monosaccharides from glucose including the pentose ribose-5-phosphate and the regulatory molecule xylulose-5-phosphate, as well as the generation of reducing equivalents for biosynthetic processes. Glycosaminoglycan metabolism and xylulose-5-phosphate synthesis from glucuronate are also annotated as parts of carbohydrate metabolism.

The digestion of dietary starch and sugars and the uptake of the resulting monosaccharides into the circulation from the small intestine are annotated as parts of the “Digestion and absorption” pathway.

Literature references

Dashty, M. (2013). A quick look at biochemistry: carbohydrate metabolism. *Clin. Biochem., 46*, 1339-52. ↗

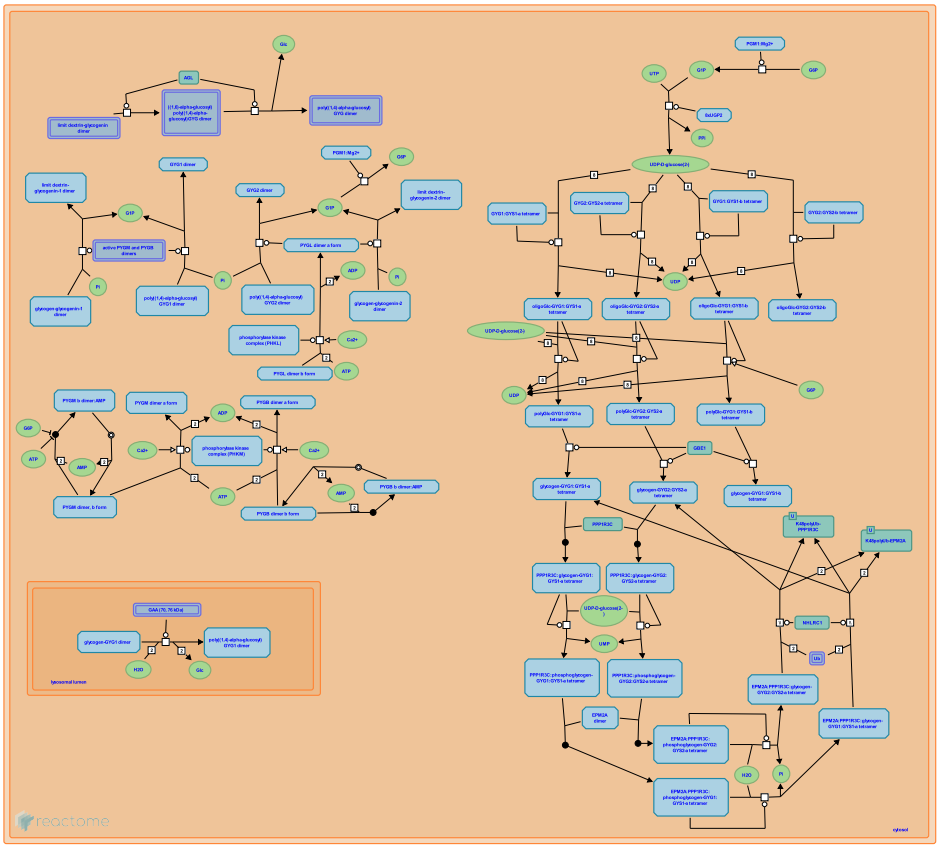
Editions

2003-11-03	Authored	Schmidt, EE., D'Eustachio, P.
2010-01-25	Revised	D'Eustachio, P.
2023-08-22	Reviewed	D'Eustachio, P.
2024-03-06	Edited	Schmidt, EE., D'Eustachio, P.

Glycogen metabolism ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-8982491



Glycogen, a highly branched glucose polymer, is formed and broken down in most human tissues, but is most abundant in liver and muscle, where it serves as a major stored fuel. Glycogen metabolism has been studied in most detail in liver and skeletal muscle. Glycogen metabolism in other tissues has not been studied as extensively, and is thought to resemble the muscle process.

Glycogen synthesis involves five reactions. The first two, conversion of glucose 6-phosphate to glucose 1-phosphate and synthesis of UDP-glucose from glucose 1-phosphate and UTP, are shared with several other pathways. The next three reactions, the auto-catalyzed synthesis of a glucose oligomer on glycogenin, the linear extension of the glucose oligomer catalyzed by glycogen synthase, and the formation of branches catalyzed by glycogen branching enzyme, are unique to glycogen synthesis. Repetition of the last two reactions generates large, extensively branched glycogen polymers. The catalysis of glycogenin glucosylation and oligoglucose chain extension by distinct isozymes in liver and nonhepatic tissues allows them to be regulated independently (Agius 2008; Bollen et al. 1998; Roach et al. 2012).

Cytosolic glycogen breakdown occurs via the same chemical steps in all tissues but is separately regulated via tissue specific isozymes and signaling pathways that enable distinct physiological fates for glycogen in liver and other tissues. Glycogen phosphorylase, which can be activated by phosphorylase kinase, catalyzes the removal of glucose residues as glucose 1-phosphate from the ends of glycogen branches. The final four residues of each branch are removed in two steps catalyzed by debranching enzyme, and further glycogen phosphorylase activity completes the process of glycogen breakdown. The first glucose residue in each branch is released as free glucose; all other residues are released as glucose 1-phosphate. The latter molecule can be converted to glucose 6-phosphate in a step shared with other pathways (Villar-Palasi & Larner 1970; Hers 1976).

Glycogen can also be taken up into lysosomes, where it is normally broken done by the action of a single enzyme, lysosomal alpha-glucosidase (GAA) (Brown et al. 1970).

Literature references

Hers, HG. (1976). The control of glycogen metabolism in the liver. *Annu Rev Biochem, 45*, 167-89. ↗

Agius, L. (2008). Glucokinase and molecular aspects of liver glycogen metabolism. *Biochem. J., 414*, 1-18. ↗

Keppens, S., Stalmans, W., Bollen, M. (1998). Specific features of glycogen metabolism in the liver. *Biochem. J., 336*, 19-31. ↗

Hurley, TD., Roach, PJ., Tagliabracci, VS., DePaoli-Roach, AA. (2012). Glycogen and its metabolism: some new developments and old themes. *Biochem. J., 441*, 763-87. ↗

Larner, J., Villar-Palasi, C. (1970). Glycogen metabolism and glycolytic enzymes. *Annu Rev Biochem, 39*, 639-72. ↗

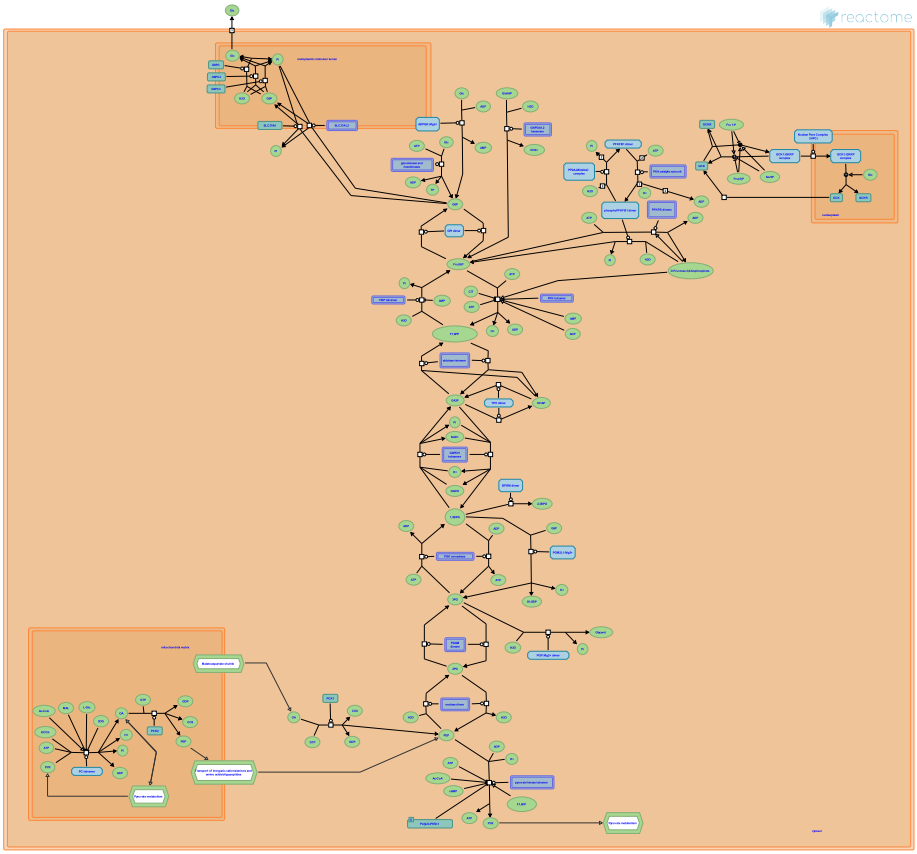
Editions

2013-07-26	Reviewed	Jassal, B.
2017-03-18	Edited	D'Eustachio, P.

Glucose metabolism ↗

Location: Metabolism of carbohydrates

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

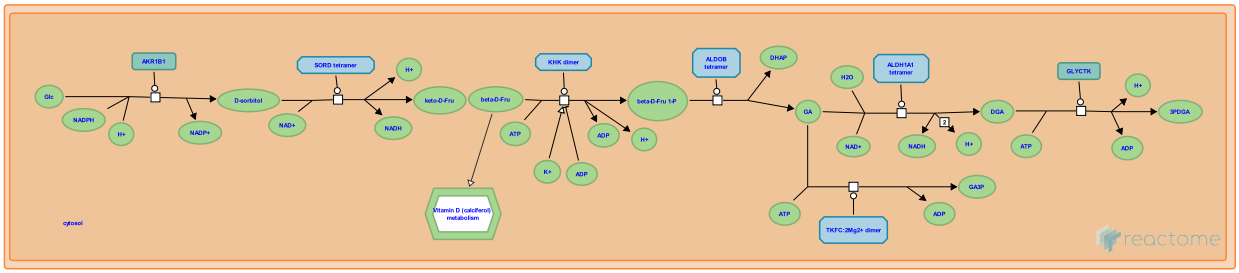
2003-02-05	Authored	Schmidt, EE.
2009-12-12	Revised	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

Fructose metabolism ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-5652084

Compartments: cytosol



Fructose is found in fruits, is one of the components of the disaccharide sucrose, and is a widely used sweetener in processed foods. Dietary fructose is catabolized in the liver via fructose 1-phosphate to yield dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, which then are converted to pyruvate via steps of canonical glycolysis (Hers & Kusaka 1953; Sillero et al. 1969). Excessive dietary intake of fructose and its metabolism have been associated with major disease risks in humans, although this issue remains controversial (Kolderup & Svihus 2015; DiNicolantonio et al. 2015; Bray 2013; Mayes 1993; Rippe & Angelopoulos 2013; van Buul et al. 2013). Fructose can also be synthesized from glucose via the polyol pathway (Hers 1960; Oates 2008). This synthetic process provides the fructose found in seminal fluid and, in other tissues, can contribute to pathologies of diabetes.

Literature references

Rippe, JM., Angelopoulos, TJ. (2013). Sucrose, high-fructose corn syrup, and fructose, their metabolism and potential health effects: what do we really know?. *Adv Nutr, 4*, 236-45. ↗

Bray, GA. (2013). Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. *Adv Nutr, 4*, 220-5. ↗

Svihus, B., Kolderup, A. (2015). Fructose Metabolism and Relation to Atherosclerosis, Type 2 Diabetes, and Obesity. *J Nutr Metab, 2015*, 823081. ↗

Brouns, FJ., Tappy, L., van Buul, VJ. (2014). Misconceptions about fructose-containing sugars and their role in the obesity epidemic. *Nutr Res Rev, 27*, 119-30. ↗

Hers, HG., Kusaka, T. (1953). [The metabolism of fructose-1-phosphate in the liver.]. *Biochim Biophys Acta, 11*, 427-37. ↗

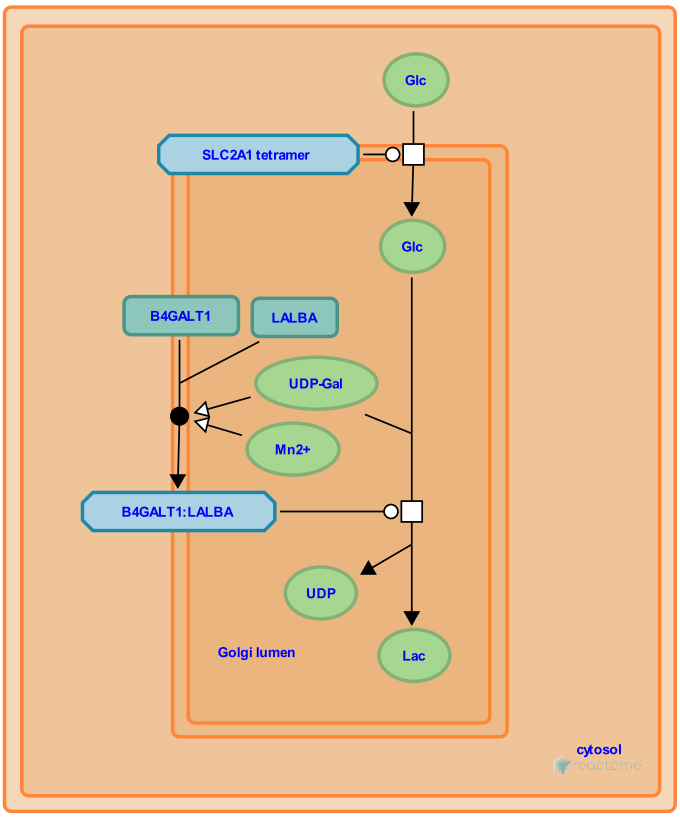
Editions

2014-11-27	Authored, Edited	D'Eustachio, P.
2015-08-28	Authored	Ribeiro, JM., Cameselle, JC.

Lactose synthesis ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-5653890



Synthesis of the disaccharide lactose takes place within the Golgi apparatus of epithelial cells of the lactating mammary gland. The synthesis itself is a single chemical reaction of free glucose and UDP-galactose to form lactose and UDP. For this reaction to occur, glucose is transported from the cytosol into the Golgi lumen, and B4GALT1 interacts with LALBA (alpha-lactalbumin) to modulate its substrate specificity (Brew and Hill 1975).

Literature references

Brew, K., Hill, RL. (1975). Lactose biosynthesis. *Rev. Physiol. Biochem. Pharmacol., 72*, 105-58. ↗

Editions

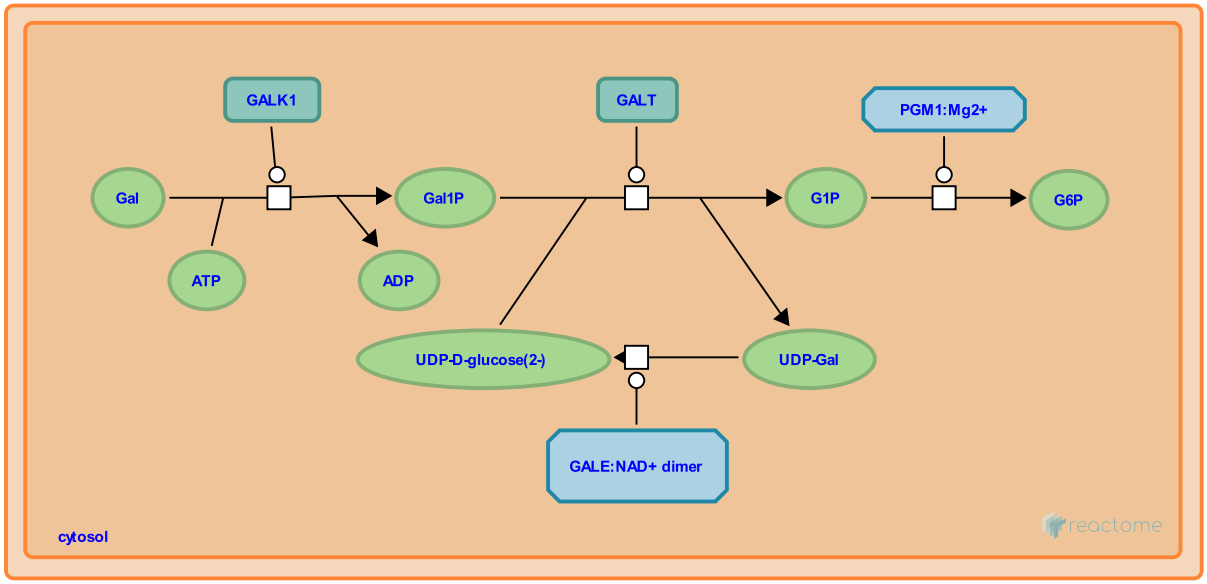
2015-01-29	Reviewed	Jassal, B.

Galactose catabolism ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-70370

Compartments: cytosol



The main sources of galactose in the human diet are milk and milk products. The disaccharide lactose from these sources is hydrolyzed in the intestine to its constituent monosaccharides, glucose and galactose. Galactose is metabolized primarily in the liver in a sequence of three reactions that yield one molecule of glucose 1-phosphate per molecule of galactose. First, it is phosphorylated to yield galactose 1-phosphate. Then, galactose 1-phosphate and UDP-glucose react to form UDP-galactose and glucose 1-phosphate, and UDP-galactose undergoes epimerization to form UDP-glucose. In a reaction shared with other pathways, glucose 1-phosphate can be converted into glucose 6-phosphate (Holton et al. 2001; Elsas and Lai 2001).

Literature references

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). Galactosemia, The Metabolic & Molecular Bases of Inherited Disease. *McGraw Hill*, 1553-1587.

Elsas, LJ., Lai, K. (2001). The molecular biology of galactosemia. *Genet Med, 1*, 40-8. ↗

Editions

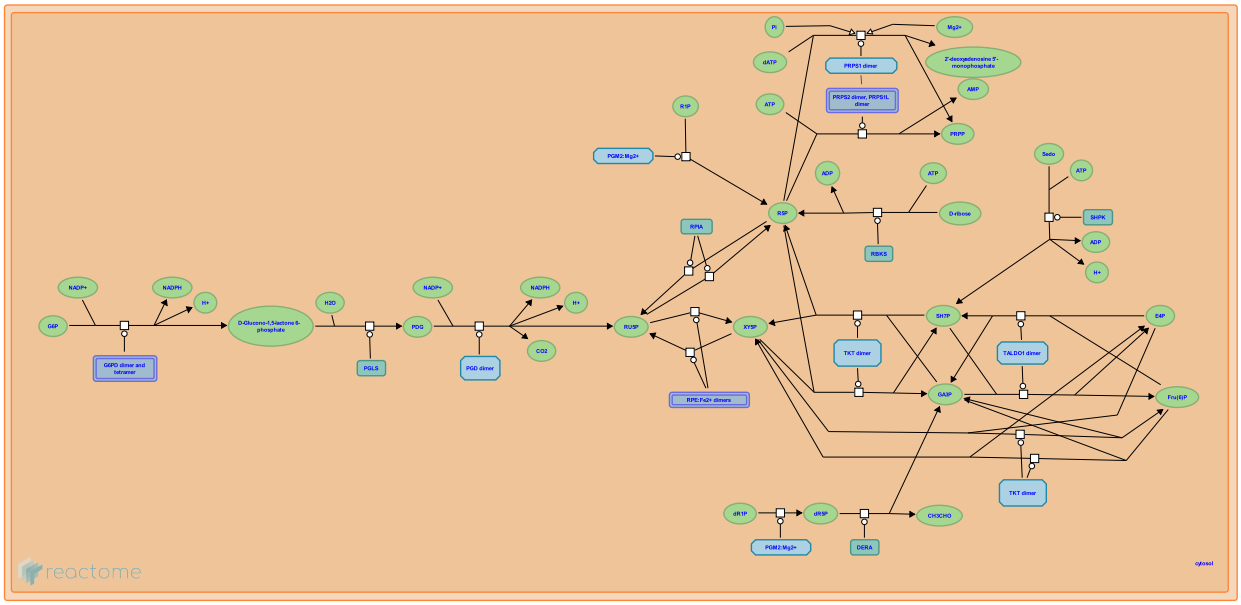
2010-01-25	Revised	D'Eustachio, P.

Pentose phosphate pathway ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-71336

Compartments: cytosol



The pentose phosphate pathway is responsible for the generation of a substantial fraction of the cytoplasmic NADPH required for biosynthetic reactions, and for the generation of ribose 5-phosphate for nucleotide synthesis. Although the pentose phosphate pathway and glycolysis are distinct, they involve three common intermediates, glucose 6-phosphate, glyceraldehyde 3-phosphate, and fructose 6-phosphate, so the two pathways are interconnected. The pentose phosphate pathway consists of eight reactions:1. Conversion glucose 6-phosphate to D-glucono-1,5-lactone 6-phosphate, with the formation of NADPH; 2. Conversion of D-glucono-1,5-lactone 6-phosphate to 6-phospho-D-gluconate; 3. Conversion of 6-phospho-D-gluconate to ribulose 5-phosphate, with the formation of NADPH; 4. Conversion of ribulose 5-phosphate to xylulose 5-phosphate; 5. Conversion of ribulose 5-phosphate to ribose 5-phosphate; 6. Rearrangement of ribose 5-phosphate and xylulose 5-phosphate to form sedoheptulose 7-phosphate and glyceraldehyde 3-phosphate; 7. Rearrangement of sedoheptulose 7-phosphate and glyceraldehyde 3-phosphate to form erythrose 4-phosphate and fructose 6-phosphate; and 8. Rearrangement of xylulose 5-phosphate and erythrose 4-phosphate to form glyceraldehyde 3-phosphate and fructose-6-phosphate.

The oxidative branch of the pentose phosphate pathway, reactions 1-3, generates NADPH and pentose 5-phosphate. The non-oxidative branch of the pathway, reactions 4-8, converts pentose 5-phosphate to other sugars.

The overall pathway can operate to generate only NADPH (glucose 6-phosphate is converted to pentose 5-phosphates, which are directed to the synthesis of fructose 6-phosphate and glyceraldehyde 3-phosphate, which in turn are converted back to glucose 6-phosphate). The reactions of the non-oxidative branch can operate to generate net amounts of ribose 5-phosphate with no production of NADPH. Net flux through this network of reactions appears to depend on the metabolic state of the cell and the nature of the biosynthetic reactions underway (Casazza and Veech 1987).

G6PD, the enzyme that catalyzes the first reaction of the pathway, is more extensively mutated in human populations than any other enzyme, pehaps because these mutant alleles confer malaria resistance (Luzzatto and Afolayan 1968). Mutations affecting other parts of the pathway are rare, though several have been described and studies of their effects have contributed to our understanding of the normal flux of metabolites through this network of reactions (Wamelink et al. 2008).

Literature references

Veech, RL., Casazza, JP. (1987). The content of pentose-cycle intermediates in liver in starved, fed ad libitum and meal-fed rats. *Biochem J, 236*, 635-41. ↗

Luzzatto, L., Afolayan, A. (1968). Enzymic properties of different types of human erythrocyte glucose-6-phosphate dehydrogenase, with characterization of two new genetic variants. *J Clin Invest, 47*, 1833-42. ↗

Wamelink, MM., Struys, EA., Jakobs, C. (2008). The biochemistry, metabolism and inherited defects of the pentose phosphate pathway: a review. *J Inherit Metab Dis, 31*, 703-17. ↗

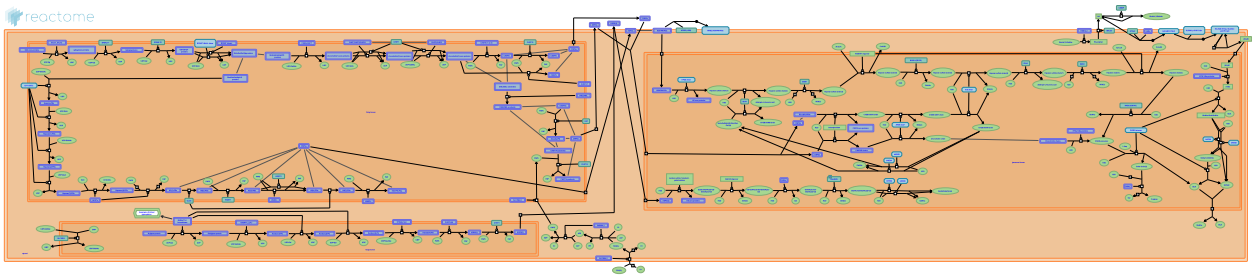
Editions

2010-01-25	Revised	D'Eustachio, P.

Glycosaminoglycan metabolism ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-1630316



Glycosaminoglycans (GAGs) are long, unbranched polysaccharides containing a repeating disaccharide unit composed of a hexosamine (either N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc)) and a uronic acid (glucuronate or iduronate). They can be heavily sulfated. GAGs are located primarily in the extracellular matrix (ECM) and on cell membranes, acting as a lubricating fluid for joints and as part of signalling processes. They have structural roles in connective tissue, cartilage, bone and blood vessels (Esko et al. 2009). GAGs are degraded in the lysosome as part of their natural turnover. Defects in the lysosomal enzymes responsible for the metabolism of membrane-associated GAGs lead to lysosomal storage diseases called mucopolysaccharidoses (MPS). MPSs are characterised by the accumulation of GAGs in lysosomes resulting in chronic, progressively debilitating disorders that in many instances lead to severe psychomotor retardation and premature death (Cantz & Gehler 1976, Clarke 2008). The biosynthesis and breakdown of the main GAGs (hyaluronate, keratan sulfate, chondroitin sulfate, dermatan sulfate and heparan sulfate) is described here.

Literature references

Cantz, M., Gehler, J. (1976). The mucopolysaccharidoses: inborn errors of glycosaminoglycan catabolism. *Hum Genet , 32*, 233-55. ↗

Kimata, K., Esko, JD., Esko, JD., Varki, A., Bertozzi, CR., Etzler, ME. et al. (2009). Proteoglycans and Sulfated Glycosaminoglycans.

Clarke, LA. (2008). The mucopolysaccharidoses: a success of molecular medicine. *Expert Rev Mol Med, 10*, e1. ↗

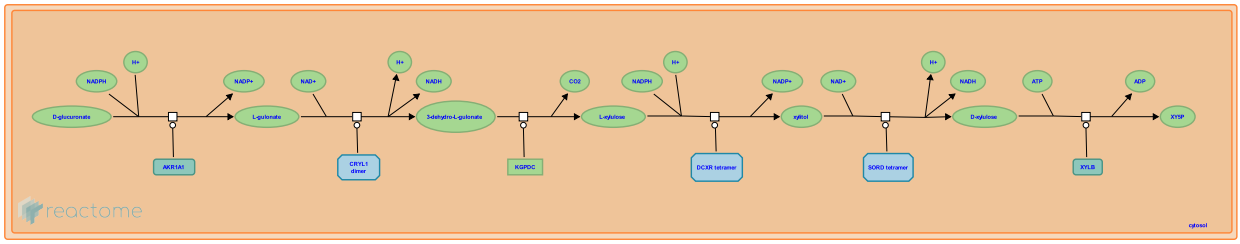
Editions

2011-10-05	Authored, Edited	Jassal, B.
2012-03-28	Reviewed	D'Eustachio, P.

Formation of xylulose-5-phosphate ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-5661270



The conversion of D-glucuronate to D-xylulose-5-phosphate, an intermediate in the pentose phosphate pathway, proceeds via L-gulonate, 3-dehydro-L-gulonate, L-xylulose, xylitol, and D-xylulose (Wamelink et al. 2008). D-glucuronate can be generated via the degradation of glucuronidated proteins. This pathway would have the effect of returning it to the pentose phosphate pathway or glycolysis.

Literature references

Wamelink, MM., Struys, EA., Jakobs, C. (2008). The biochemistry, metabolism and inherited defects of the pentose phosphate pathway: a review. *J Inherit Metab Dis, 31*, 703-17. ↗

Editions

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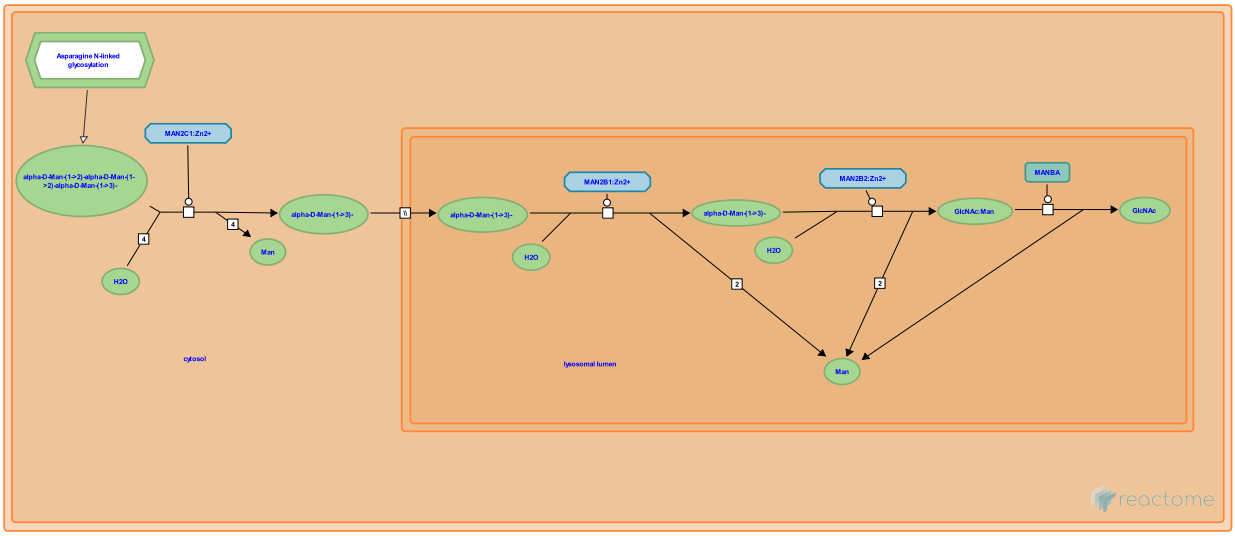
2015-08-14	Reviewed	Jassal, B.

Lysosomal oligosaccharide catabolism ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-8853383



N-Glycosylation is one of the most common co- and posttranslational modifications of eukaryotic proteins occurring in the ER lumen. N-glycosylation plays pivotal roles in protein folding and intra- or inter-cellular trafficking of N-glycosylated proteins. Quality control mechanisms in the ER sift out incorrectly-folded proteins from correctly-folded proteins, the former then destined for degradation. Incorrectly-folded N-glycans are exported to the cytosol where the process of degradation begins. Once the unfolded protein is cleaved from the oligosaccharide (forming free oligosaccharides, fOS), step-wise degradation of mannose moieties, both in the cytosol (Suzuki & Harada 2014) and then in the lysosome (Aronson & Kuranda 1989, Winchester 2005), results in complete degradation. Breakdown must be complete to avoid lysosomal storage diseases that occur when fragments as small as dimers are left undigested.

Literature references

Masahara-Negishi, Y., Harada, Y., Suzuki, T. (2015). Cytosolic-free oligosaccharides are predominantly generated by the degradation of dolichol-linked oligosaccharides in mammalian cells. *Glycobiology, 25*, 1196-205. ↗

Aronson NN, Jr., Kuranda, MJ. (1989). Lysosomal degradation of Asn-linked glycoproteins. *FASEB J, 3*, 2615-22. ↗

Winchester, B. (2005). Lysosomal metabolism of glycoproteins. *Glycobiology, 15*, 1R-15R. ↗

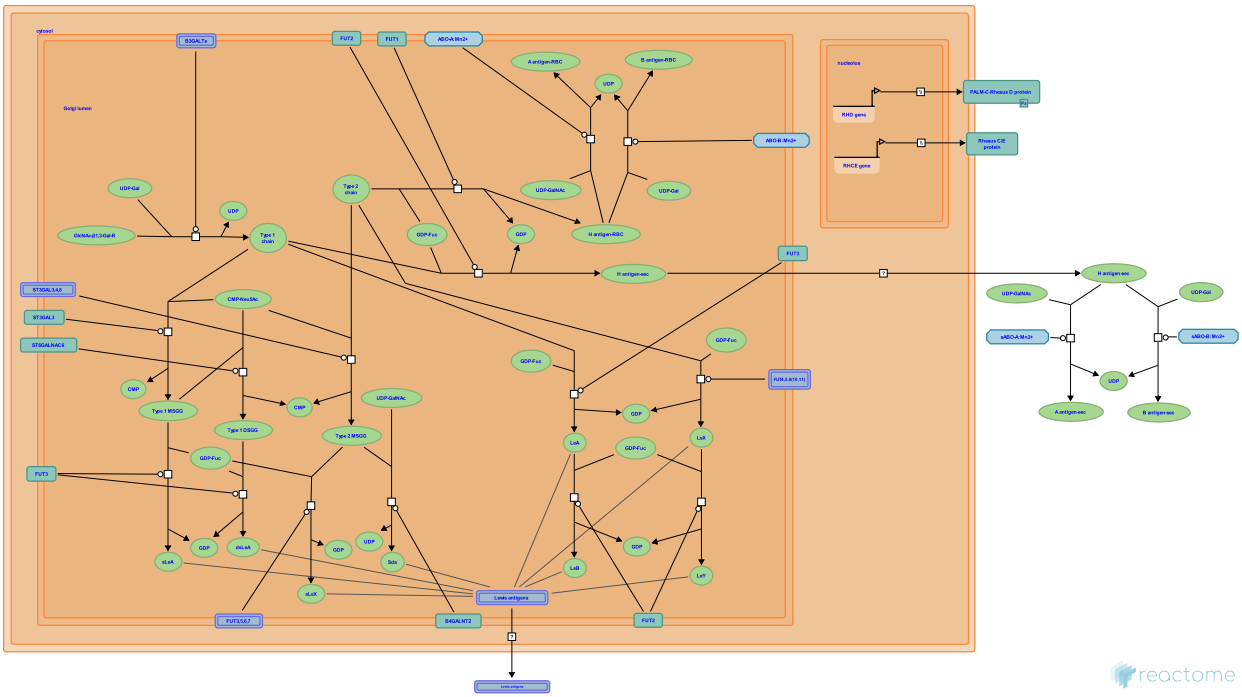
Editions

2016-01-22	Authored, Edited	Jassal, B.
2016-01-26	Reviewed	D'Eustachio, P.

Blood group systems biosynthesis ↗

Location: Metabolism of carbohydrates

Stable identifier: R-HSA-9033658



The association between blood type and disease has been studied since the beginning of the 20th Century (Anstee 2010, Ewald & Sumner 2016). Landsteiner's discovery of blood groups in 1900 was based on agglutination patterns of red blood cells when blood types from different donors were mixed (Landsteiner 1931, Owen 2000, Tan & Graham 2013). His work is the basis of routine compatibility testing and transfusion practices today. The immune system of patients receiving blood transfusions will attack any donor red blood cells that contain antigens that differ from their self-antigens. Therefore, matching blood types is essential for safe blood transfusions. Landsteiner's classification of the ABO blood groups confirmed that antigens were inherited characteristics. In the 1940s, it was established that the specificity of blood group antigens was determined by their unique oligosaccharide structures. Since then, exponential advances in technology have resulted in the identification of over 300 blood group antigens, classified into more than 35 blood group systems by the International Society of Blood Transfusion (ISBT) (Storry et al. 2016).

Blood group antigens comprise either a protein portion or oligosaccharide sequence attached on a glycolipid or glycoprotein. The addition of one or more specific sugar molecules to this oligosaccharide sequence at specific positions by a variety of glycosyltransferases results in the formation of mature blood group antigens. The genes that code for glycosytransferases can contain genetic changes that produce antigenic differences, resulting in new antigens or loss of expression. Blood group antigens are found on red blood cells (RBCs), platelets, leukocytes, and plasma proteins and also exist in soluble form in bodily secretions such as breast milk, seminal fluid, saliva, sweat, gastric secretions and urine. Blood groups are implicated in many diseases such as those related to malignancy (Rummel & Ellsworth 2016), the cardiovascular system (Liumbruno & Franchini 2013), metabolism (Meo et al. 2016, Ewald & Sumner 2016) and infection (Rios & Bianco 2000, McCullough 2014). The most important and best-studied blood groups are the ABO, Lewis and Rhesus systems. The biosynthesis of the antigens in these systems is described in this section.

Literature references

Ewald, DR., Sumner, SC. (2016). Blood type biochemistry and human disease. *Wiley Interdiscip Rev Syst Biol Med, 8*, 517-535. ↗

Ellsworth, RE., Rummel, SK. (2016). The role of the histoblood ABO group in cancer. *Future Sci OA, 2*, FSO107. ↗

Flegel, WA., Moulds, JM., van der Schoot, CE., Daniels, G., Storry, JR., Nogues, N. et al. (2016). International society of blood transfusion working party on red cell immunogenetics and terminology: report of the Seoul and London meetings. *ISBT Sci Ser, 11*, 118-122. ↗

Landsteiner, K. (1931). INDIVIDUAL DIFFERENCES IN HUMAN BLOOD. *Science, 73*, 403-9. ↗

Owen, R. (2000). Karl Landsteiner and the first human marker locus. *Genetics, 155*, 995-8. ↗

Editions

2017-12-27	Authored, Edited	Jassal, B.
2018-12-17	Reviewed	Matsui, T.

Table of Contents