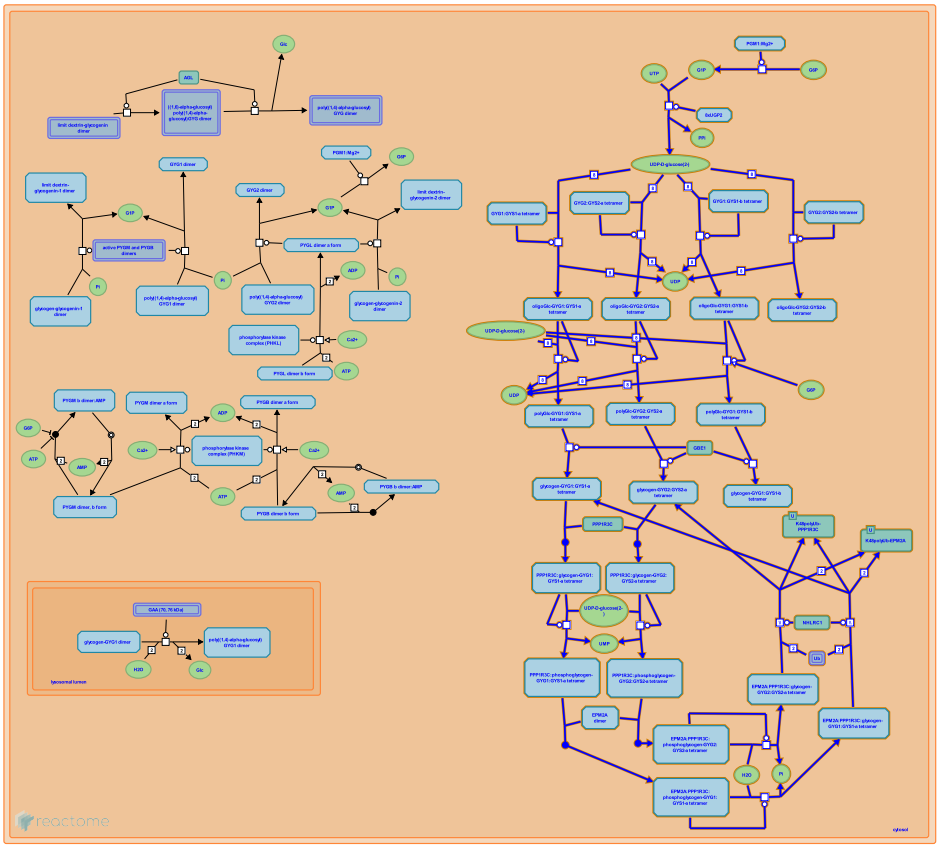
Glycogen synthesis



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09/05/2024

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. ↗

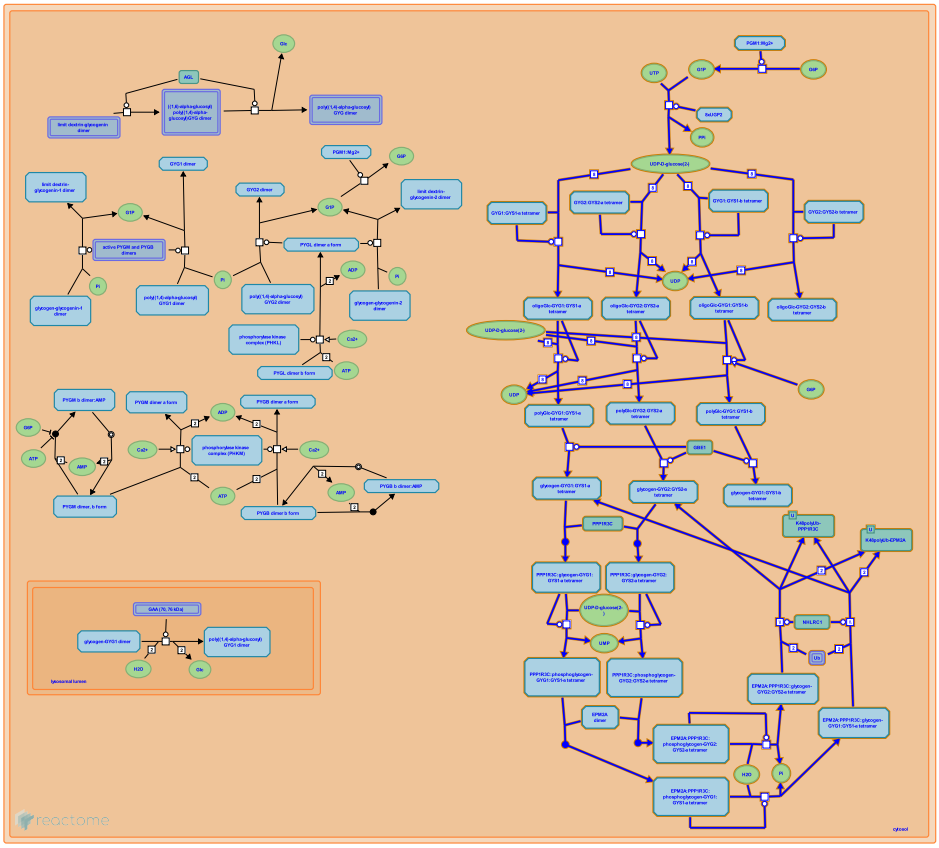
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Glycogen synthesis ↗

Stable identifier: R-HSA-3322077



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 muscle, although considerable experimental data are available concerning these reactions in liver as well. 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).

Literature references

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. ↗

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

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

Editions

2010-01-22	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2013-08-25	Revised	D'Eustachio, P.
2014-02-19	Revised	D'Eustachio, P.
2017-03-18	Edited	D'Eustachio, P.

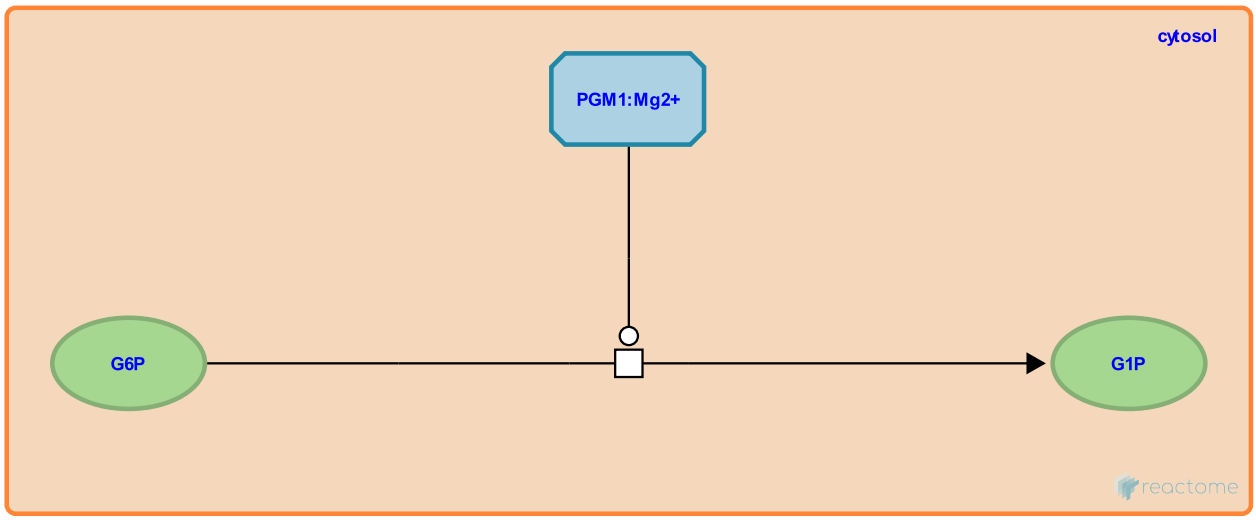
PGM1:Mg2+ isomerises G6P to G1P ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-9638127

Type: transition

Compartments: cytosol



Cytosolic phosphoglucomutase1 (PGM1) catalyses the reversible conversion of glucose 6-phosphate (G6P) to glucose 1-phosphate (G1P) (March et al. 1993; Quick et al. 1974).

Followed by: UTP + D-glucose 1-phosphate <=> pyrophosphate + UDP-glucose

Literature references

Lovegrove, JU., Whitehouse, DB., Edwards, YH., Hopkinson, DA., March, RE., Ives, JH. et al. (1993). The classical human phosphoglucomutase (PGM1) isozyme polymorphism is generated by intragenic recombination. *Proc Natl Acad Sci U S A, 90*, 10730-3. ↗

Quick, CB., Harris, H., Fisher, RA. (1974). A kinetic study of the isozymes determined by the three human phosphoglucomutase loci PGM1, PGM2, and PGM3. *Eur J Biochem, 42*, 511-7. ↗

Editions

2010-01-22	Revised	D'Eustachio, P.
2017-01-12	Edited, Revised	Jassal, B.

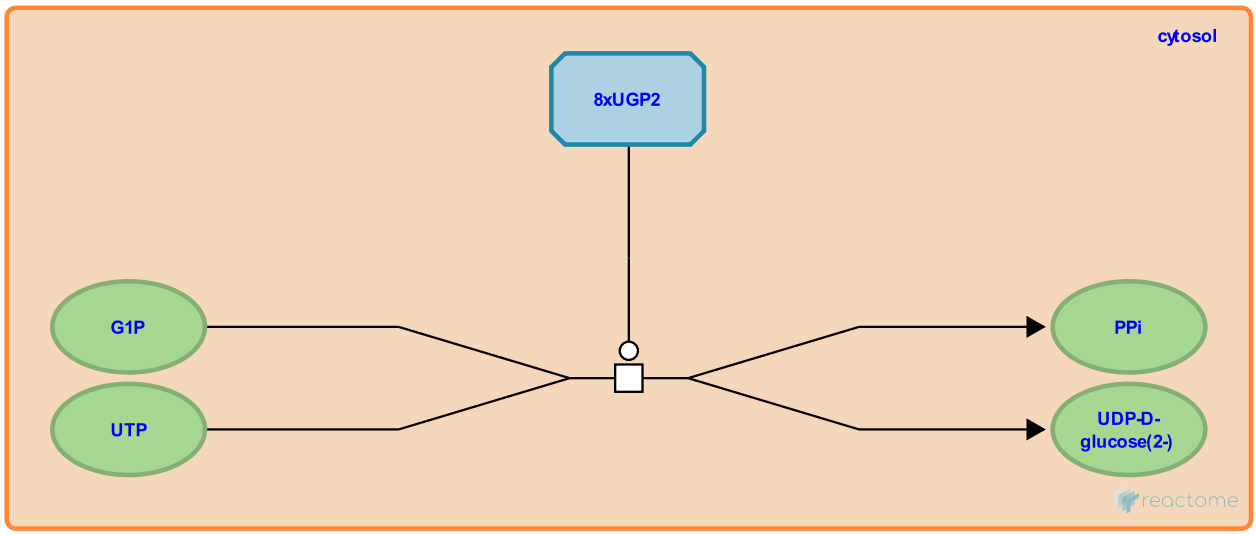
UTP + D-glucose 1-phosphate <=> pyrophosphate + UDP-glucose ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-70286

Type: transition

Compartments: cytosol



Cytosolic UDP-glucose pyrophosphorylase 2 (UGP2) catalyzes the reaction of UTP and glucose 1-phosphate to form UDP glucose and pyrophosphate (Knop and Hansen 1970; Duggleby et al. 1996). UGP2 is inferred to occur in the cell as a homooctamer from studies of its bovine homologue (Levine et al. 1969).

Preceded by: PGM1:Mg2+ isomerises G6P to G1P

Followed by: Autoglucosylation of GYG2 complexed with GYS2-b, Autoglucosylation of GYG2 complexed with GYS2-a, Autoglucosylation of GYG1 complexed with GYS1-a, Autoglucosylation of GYG1 complexed with GYS1-b

Literature references

Hageman, E., Levine, S., Gillett, TA., Hansen, RG. (1969). Uridine diphosphate glucose pyrophosphorylase. II. *J Biol Chem, 244*, 5729-34. ↗

Hansen, RG., Knop, JK. (1970). Uridine diphosphate glucose pyrophosphorylase. IV. Crystallization and properties of the enzyme from human liver. *J Biol Chem, 245*, 2499-504. ↗

Duggleby, RG., Peng, HL., Chao, YC., Chang, HY., Huang, JG. (1996). Sequence differences between human muscle and liver cDNAs for UDPglucose pyrophosphorylase and kinetic properties of the recombinant enzymes expressed in Escherichia coli. *Eur J Biochem, 235*, 173-9. ↗

Editions

2008-05-28	Reviewed	D'Eustachio, P.
2010-01-22	Revised	D'Eustachio, P.

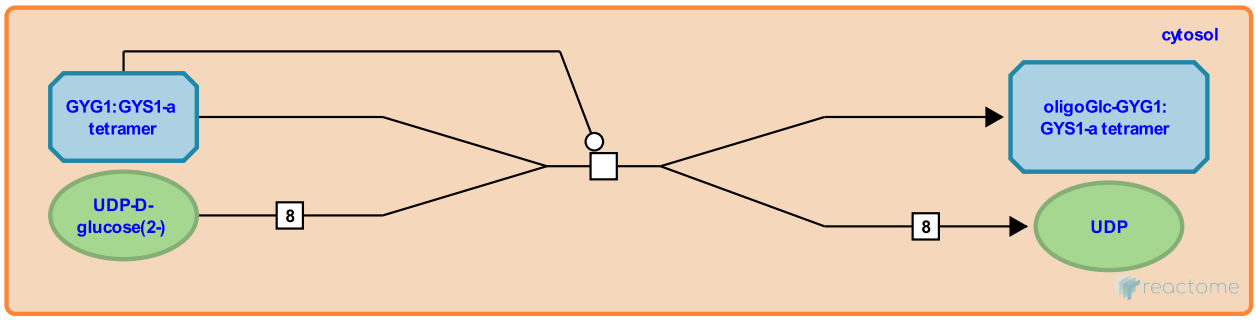
Autoglucosylation of GYG1 complexed with GYS1-a ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3322025

Type: transition

Compartments: cytosol



Glycogenin 1 (GYG1) catalyzes its autoglycosylation reaction with UDP-glucose to form oligo (1,4)-alpha-D-glucosyl GYG1 (Moslemi et al. 2010). The oligosaccharide is annotated here as containing four glucose residues. Glycogenin occurs as a homodimer complexed with two molecules of glycogen synthase 1 (GYS1), here in an unphosphorylated (a) form (Roach et al. 2012).

Preceded by: UTP + D-glucose 1-phosphate <=> pyrophosphate + UDP-glucose

Followed by: GYS1 catalyzes the polyglucosylation of oligoGlc-GYG1

Literature references

Nilsson, J., Oldfors, A., Lindberg, C., Moslemi, AR., Andersson, B., Tajsharghi, H. (2010). Glycogenin-1 deficiency and inactivated priming of glycogen synthesis. *N. Engl. J. Med., 362,* 1203-10. ↗

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. ↗

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

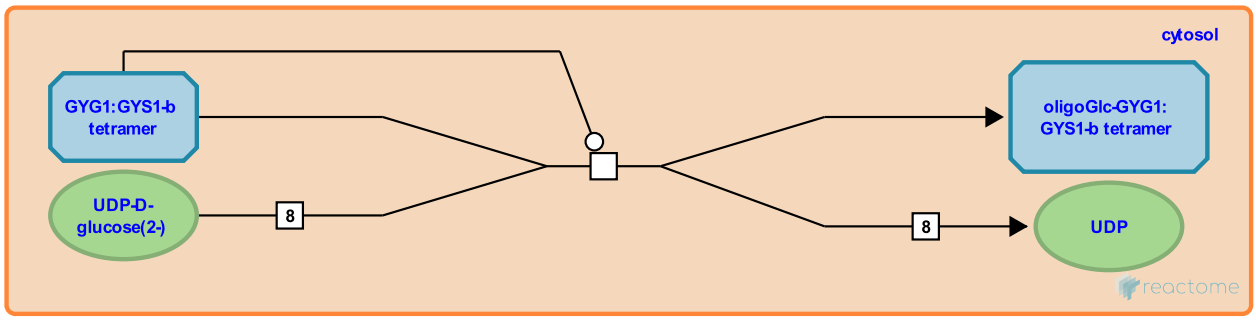
Autoglucosylation of GYG1 complexed with GYS1-b ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3322003

Type: transition

Compartments: cytosol



Glycogenin 1 (GYG1) catalyzes its autoglycosylation reaction with UDP-glucose to form oligo (1,4)-alpha-D-glucosyl GYG1 (Moslemi et al. 2010). The oligosaccharide is annotated here as containing four glucose residues. Glycogenin occurs as a homodimer complexed with two molecules of glycogen synthase 1 (GYS1), here in a phosphorylated (b) form (Roach et al. 2012).

Preceded by: UTP + D-glucose 1-phosphate <=> pyrophosphate + UDP-glucose

Followed by: Phosphorylated GYS1 catalyzes the polyglucosylation of oligoGlc-GYG1

Literature references

Nilsson, J., Oldfors, A., Lindberg, C., Moslemi, AR., Andersson, B., Tajsharghi, H. (2010). Glycogenin-1 deficiency and inactivated priming of glycogen synthesis. *N. Engl. J. Med., 362,* 1203-10. ↗

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. ↗

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

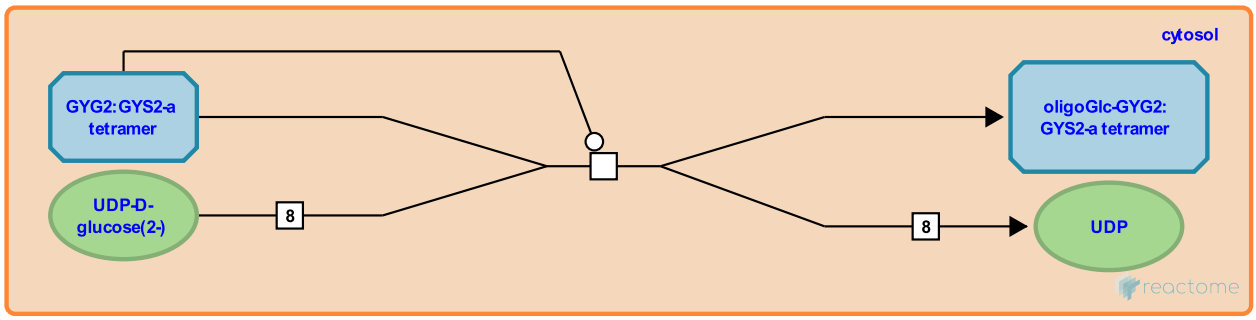
Autoglucosylation of GYG2 complexed with GYS2-a ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3322014

Type: transition

Compartments: cytosol



Glycogenin 2 (GYG2) catalyzes its autoglycosylation reaction with UDP-glucose to form oligo (1,4)-alpha-D-glucosyl GYG2 (Mu et al. 1997). The oligosaccharide is annotated here as containing four glucose residues. Glycogenin occurs as a homodimer complexed with two molecules of glycogen synthase 1 (GYS2), here in a unphosphorylated (a) form (Roach et al. 2012).

Preceded by: UTP + D-glucose 1-phosphate <=> pyrophosphate + UDP-glucose

Followed by: GYS2 catalyzes the polyglucosylation of oligoGlc-GYG2

Literature references

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. ↗

Mu, J., Roach, PJ., Skurat, AV. (1997). Glycogenin-2, a novel self-glucosylating protein involved in liver glycogen biosynthesis. *J Biol Chem, 272*, 27589-97. ↗

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

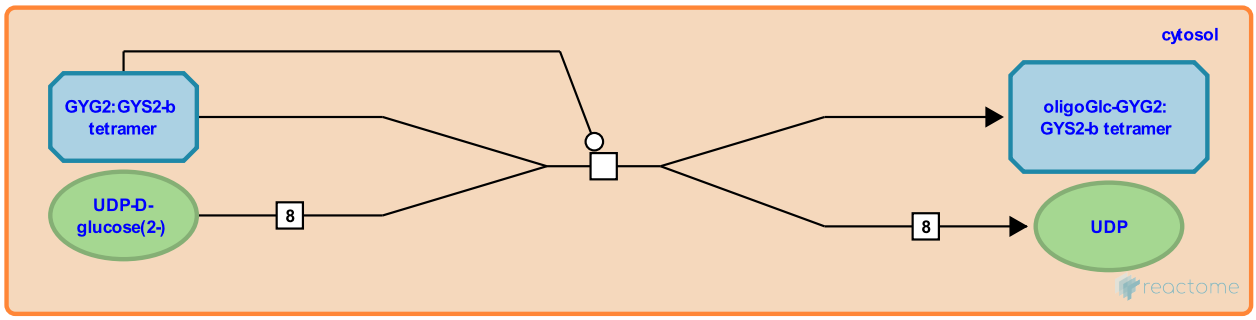
Autoglucosylation of GYG2 complexed with GYS2-b ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3322019

Type: transition

Compartments: cytosol



Glycogenin 2 (GYG2) catalyzes its autoglycosylation reaction with UDP-glucose to form oligo (1,4)-alpha-D-glucosyl GYG2 (Mu et al. 1997). The oligosaccharide is annotated here as containing four glucose residues. Glycogenin occurs as a homodimer complexed with two molecules of glycogen synthase 1 (GYS2), here in a phosphorylated (b) form (Roach et al. 2012).

Preceded by: UTP + D-glucose 1-phosphate <=> pyrophosphate + UDP-glucose

Literature references

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. ↗

Mu, J., Roach, PJ., Skurat, AV. (1997). Glycogenin-2, a novel self-glucosylating protein involved in liver glycogen biosynthesis. *J Biol Chem, 272*, 27589-97. ↗

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

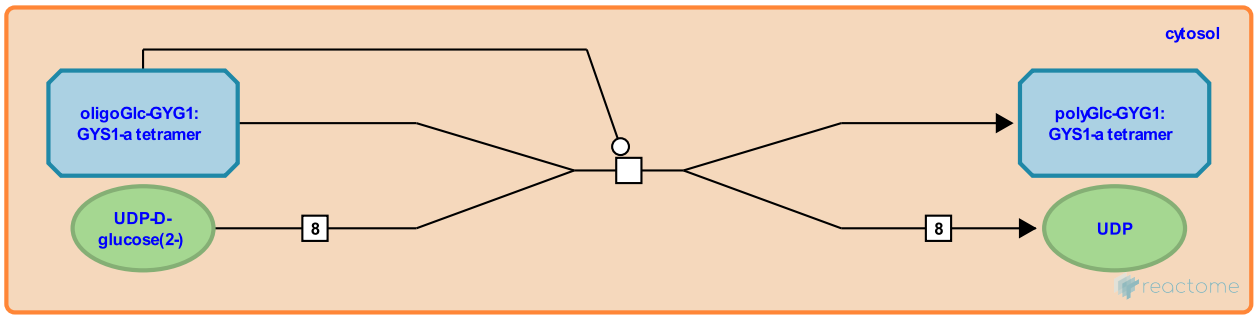
GYS1 catalyzes the polyglucosylation of oligoGlc-GYG1 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3322001

Type: transition

Compartments: cytosol



Unphosphorylated glycogen synthase 1 (GYS1-a) complexed with oligo-D-glucose-GYG1 catalyzes the polyglucosylation of the latter. (Here the addition of four glucose residues is annotated.) (Cameron et al. 2009; Roach et al. 2012).

Preceded by: Autoglucosylation of GYG1 complexed with GYS1-a

Followed by: GBE1 catalyzes branch formation in polyGlc-GYG1 complexed with GYS1-a

Literature references

Utgikar, R., Robinson, BH., Cameron, JM., Chiasson, D., Halliday, W., Ackerley, CA. et al. (2009). Identification of a novel mutation in GYS1 (muscle-specific glycogen synthase) resulting in sudden cardiac death, that is diagnosable from skin fibroblasts. *Mol. Genet. Metab., 98*, 378-82. ↗

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. ↗

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

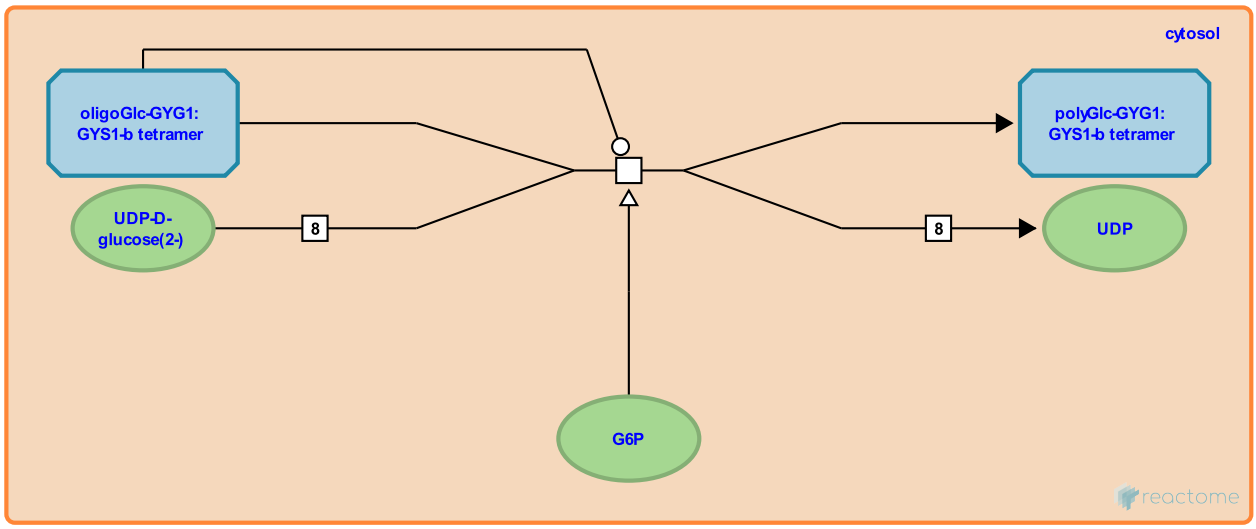
Phosphorylated GYS1 catalyzes the polyglucosylation of oligoGlc-GYG1 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3322041

Type: transition

Compartments: cytosol



Phosphorylated glycogen synthase 1 (GYS1-b) complexed with oligo-D-glucose-GYG1 catalyzes the polyglucosylation of the latter. (Here the addition of four glucose residues is annotated.) This reaction is allosterically activated by glucose-6-phosphate (G6P) (Cameron et al. 2009; Roach et al. 2012). Glucose-6-phosphate (G6P) activates the phosphorylated ("b") form of GYS1 ("muscle") glycogen synthase (Roach et al. 2012).

Preceded by: Autoglucosylation of GYG1 complexed with GYS1-b

Followed by: GBE1 catalyzes branch formation in polyGlc-GYG1 complexed with GYS1-b

Literature references

Utgikar, R., Robinson, BH., Cameron, JM., Chiasson, D., Halliday, W., Ackerley, CA. et al. (2009). Identification of a novel mutation in GYS1 (muscle-specific glycogen synthase) resulting in sudden cardiac death, that is diagnosable from skin fibroblasts. *Mol. Genet. Metab., 98*, 378-82. ↗

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. ↗

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

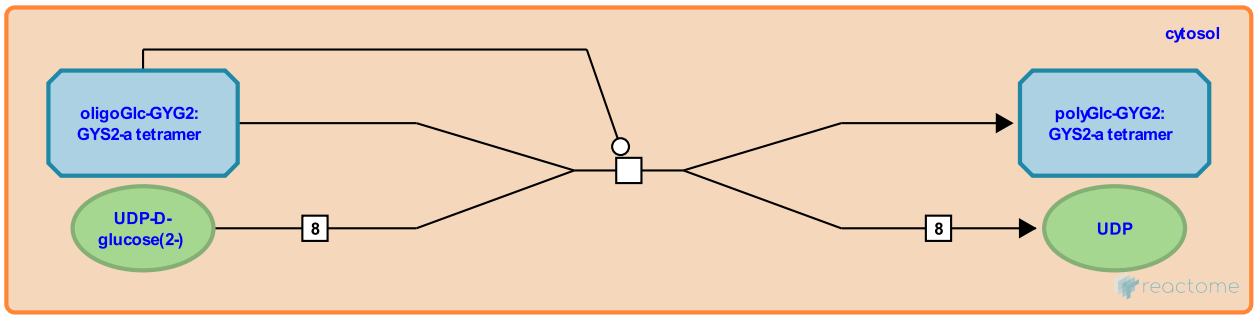
GYS2 catalyzes the polyglucosylation of oligoGlc-GYG2

Location: Glycogen synthesis

Stable identifier: R-HSA-3322009

Type: transition

Compartments: cytosol



Unphosphorylated glycogen synthase 2 (GYS2-a) complexed with oligo-D-glucose-GYG2 catalyzes the polyglucosylation of the latter. (Here the addition of four glucose residues is annotated.) (Orho et al. 1998; Roach et al. 2012).

Preceded by: Autoglucosylation of GYG2 complexed with GYS2-a

Followed by: GBE1 catalyzes branch formation in polyGlc-GYG2 complexed with GYS2-a

Literature references

Aynsley-Green, A., Orho, M., Gannon, MC., Nuttall, FQ., Blumel, P., Bosshard, NU. et al. (1998). Mutations in the liver glycogen synthase gene in children with hypoglycemia due to glycogen storage disease type 0. *J Clin Invest, 102* , 507-15.

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.

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

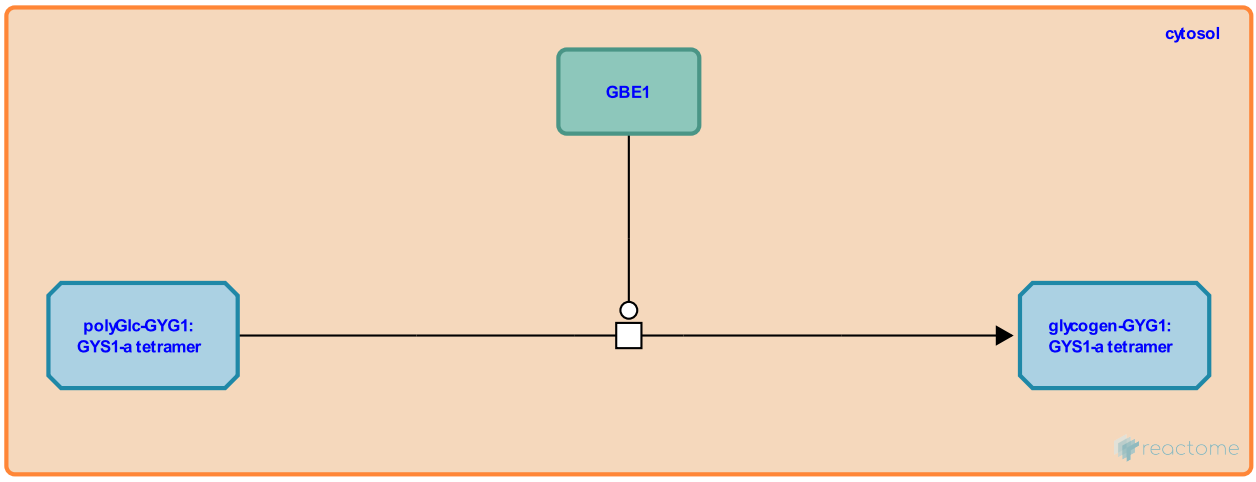
GBE1 catalyzes branch formation in polyGlc-GYG1 complexed with GYS1-a

Location: Glycogen synthesis

Stable identifier: R-HSA-3322005

Type: transition

Compartments: cytosol



Cytosolic glycogen branching enzyme (GBE1) associated with glycogen granules transfers terminal alpha(1,4) glucose blocks to form alpha(1,6) branches on growing glycogen molecules formed on glycogenin 1 (GYG1) complexed with unphosphorylated glycogen synthase 1 (GYS1-a) (Bao et al. 1996; Roach et al. 2012).

Preceded by: GYS1 catalyzes the polyglucosylation of oligoGlc-GYG1

Followed by: PPP1R3C binds to glycogen:GYG1:GYS1

Literature references

Wu, JY., Chen, Y-T., Kishnani, P., Bao, Y. (1996). Hepatic and neuromuscular forms of glycogen storage disease type IV caused by mutations in the same glycogen-branching enzyme gene. *J Clin Invest, 97*, 941-8.

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.

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

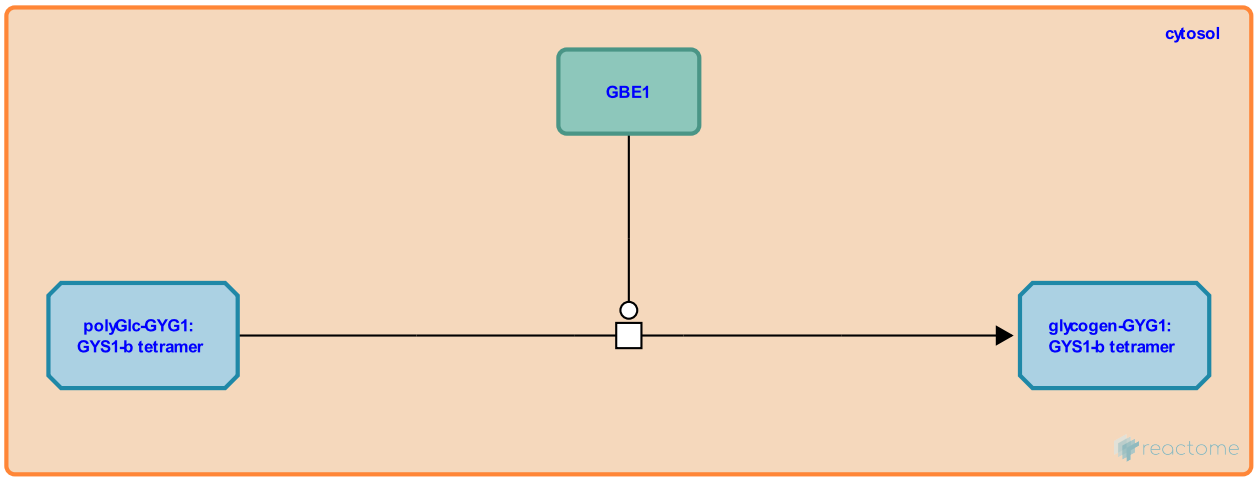
GBE1 catalyzes branch formation in polyGlc-GYG1 complexed with GYS1-b

Location: Glycogen synthesis

Stable identifier: R-HSA-3322057

Type: transition

Compartments: cytosol



Cytosolic glycogen branching enzyme (GBE1) associated with glycogen granules transfers terminal alpha(1,4) glucose blocks to form alpha(1,6) branches on growing glycogen molecules formed on glycogenin 1 (GYG1) complexed with phosphorylated glycogen synthase 1 (GYS1-b) (Bao et al. 1996; Roach et al. 2012).

Preceded by: Phosphorylated GYS1 catalyzes the polyglucosylation of oligoGlc-GYG1

Literature references

Wu, JY., Chen, Y-T., Kishnani, P., Bao, Y. (1996). Hepatic and neuromuscular forms of glycogen storage disease type IV caused by mutations in the same glycogen-branching enzyme gene. *J Clin Invest, 97*, 941-8.

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.

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

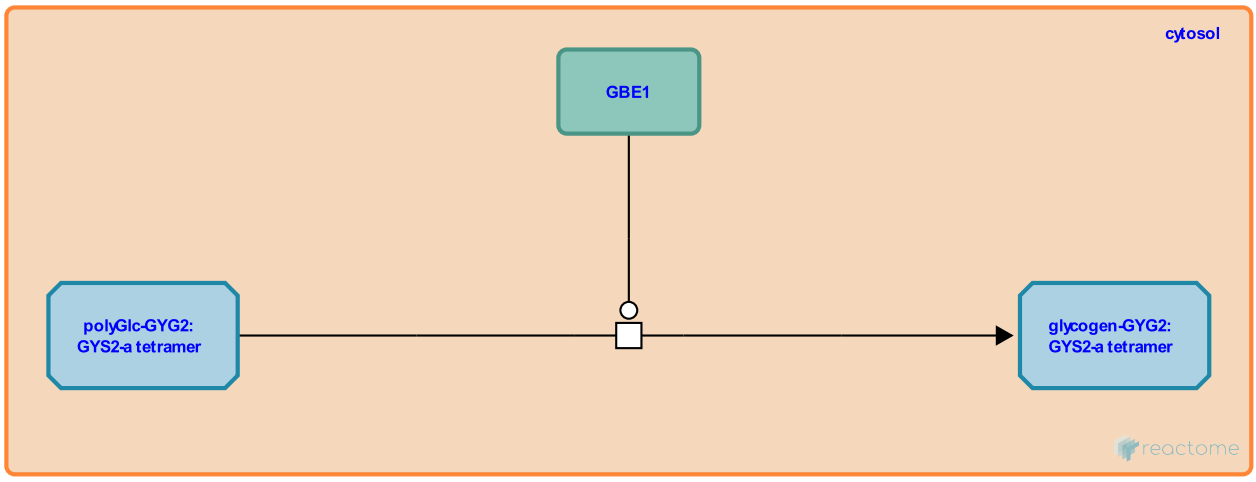
GBE1 catalyzes branch formation in polyGlc-GYG2 complexed with GYS2-a ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3322016

Type: transition

Compartments: cytosol



Cytosolic glycogen branching enzyme (GBE1) associated with glycogen granules transfers terminal alpha(1,4) glucose blocks to form alpha(1,6) branches on growing glycogen molecules formed on glycogenin 2 (GYG2) complexed with unphosphorylated glycogen synthase 2 (GYS2-a) (Bao et al. 1996; Roach et al. 2012).

Preceded by: GYS2 catalyzes the polyglucosylation of oligoGlc-GYG2

Followed by: PPP1R3C binds to glycogen:GYG2:GYS2

Literature references

Wu, JY., Chen, Y-T., Kishnani, P., Bao, Y. (1996). Hepatic and neuromuscular forms of glycogen storage disease type IV caused by mutations in the same glycogen-branching enzyme gene. *J Clin Invest, 97*, 941-8. ↗

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. ↗

Editions

2013-05-03	Revised	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.

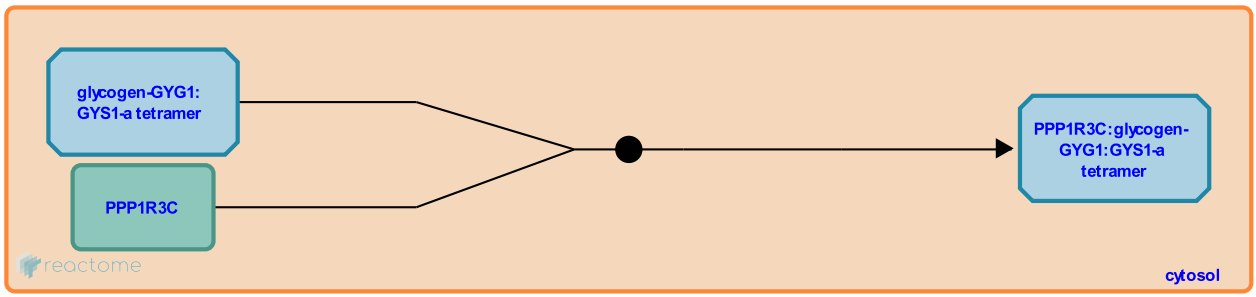
PPP1R3C binds to glycogen:GYG1:GYS1 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3781023

Type: binding

Compartments: cytosol



Protein phosphatase 1 regulatory subunit 3C (PPP1R3C, PTG) binds to glycogen particles containing GYG1 (glycogenin 1) and GYS1 (glycogen synthase 1). PPP1R3C appears to function as a scaffolding protein to mediate association of other proteins with glycogen granules and to promote the synthesis of glycogen (Worby et al. 2008).

Preceded by: GBE1 catalyzes branch formation in polyGlc-GYG1 complexed with GYS1-a

Followed by: GYS1 catalyzes the incorporation of phosphoglucose into glycogen-GYG1

Literature references

Gentry, MS., Worby, CA., Dixon, JE. (2008). Malin decreases glycogen accumulation by promoting the degradation of protein targeting to glycogen (PTG). *J. Biol. Chem., 283*, 4069-76. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.

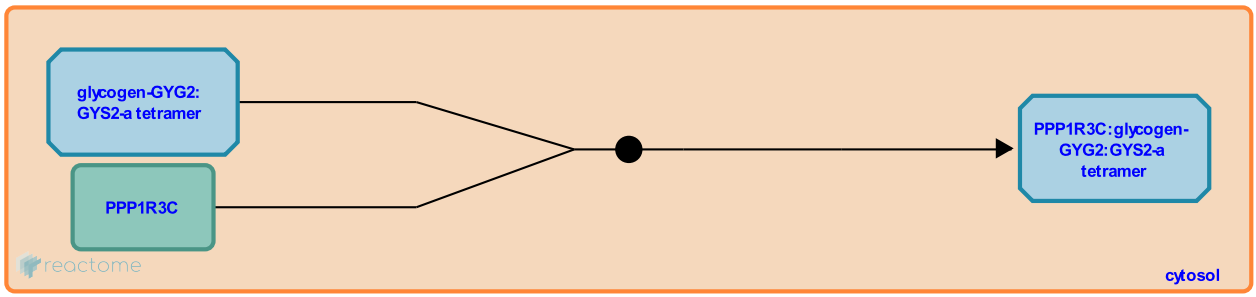
PPP1R3C binds to glycogen:GYG2:GYS2

Location: Glycogen synthesis

Stable identifier: R-HSA-3780997

Type: binding

Compartments: cytosol



Protein phosphatase 1 regulatory subunit 3C (PPP1R3C, PTG) binds to glycogen particles containing GYG2 (glycogenin 2) and GYS2 (glycogen synthase 2). PPP1R3C appears to function as a scaffolding protein to mediate association of other proteins with glycogen granules and to promote the synthesis of glycogen (Worby et al. 2008). This reaction, involving GYG and GYS isoforms largely expressed in the liver has not been studied in detail but is inferred from the better-characterized one involving GYG1- and GYS1-containing glycogen particles ("muscle" isoforms, widely expressed in the body outside the liver).

Preceded by: GBE1 catalyzes branch formation in polyGlc-GYG2 complexed with GYS2-a

Followed by: GYS2 catalyzes the incorporation of phosphoglucose into glycogen-GYG2

Literature references

Gentry, MS., Worby, CA., Dixon, JE. (2008). Malin decreases glycogen accumulation by promoting the degradation of protein targeting to glycogen (PTG). *J. Biol. Chem., 283*, 4069-76.

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.

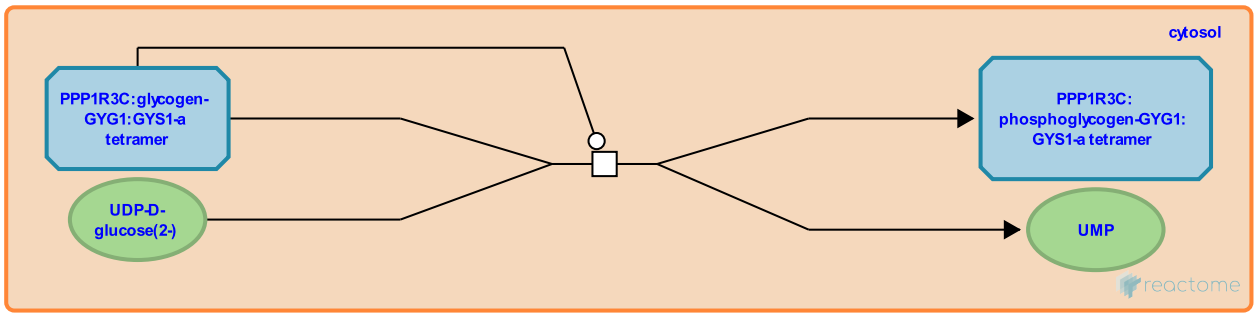
GYS1 catalyzes the incorporation of phosphoglucose into glycogen-GYG1 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3781024

Type: transition

Compartments: cytosol



Glycogen synthase 1 (GYS1) catalyzes the incorporation of phosphoglucose into the glycogen-GYG1 molecules with which it is associated in a cytosolic glycogen granule. This reaction occurs at a low rate, yielding approximately one molecule of glucose phosphorylated at its C2, C3, or C6 positions incorporated into a growing glycogen polymer per ten thousand glucose molecules incorporated (DePaoli-Roach et al. 2015; Irimia et al. 2015; Nitschke et al. 2013; Tagliabracci et al. 2011). The function of these small amounts of phosphoglucose in normal glycogen remains to be established.

Preceded by: PPP1R3C binds to glycogen:GYG1:GYS1

Followed by: EPM2A dimer binds PPP1R3C:phosphoglycogen-GYG1 complex

Literature references

Ishihara, M., Segvich, DM., Heiss, C., Roach, PJ., Contreras, CJ., Azadi, P. et al. (2015). Glycogen phosphomonoester distribution in mouse models of the progressive myoclonic epilepsy, Lafora disease. *J. Biol. Chem., 290*, 841-50. ↗

Zhao, X., Schmieder, P., Wang, P., Wang, T., Awrey, DE., Girard, JM. et al. (2013). Hyperphosphorylation of glucosyl C6 carbons and altered structure of glycogen in the neurodegenerative epilepsy Lafora disease. *Cell Metab., 17*, 756-67. ↗

Ishihara, M., Hurley, TD., Glushka, J., Heiss, C., Karthik, C., Roach, PJ. et al. (2011). Phosphate incorporation during glycogen synthesis and Lafora disease. *Cell Metab., 13*, 274-82. ↗

Segvich, DM., Meyer, CM., Roach, PJ., Irimia, JM., Tagliabracci, VS., DePaoli-Roach, AA. (2015). Muscle Glycogen Remodeling and Glycogen Phosphate Metabolism following Exhaustive Exercise of Wild Type and Laforin Knockout Mice. *J. Biol. Chem., 290*, 22686-98. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.

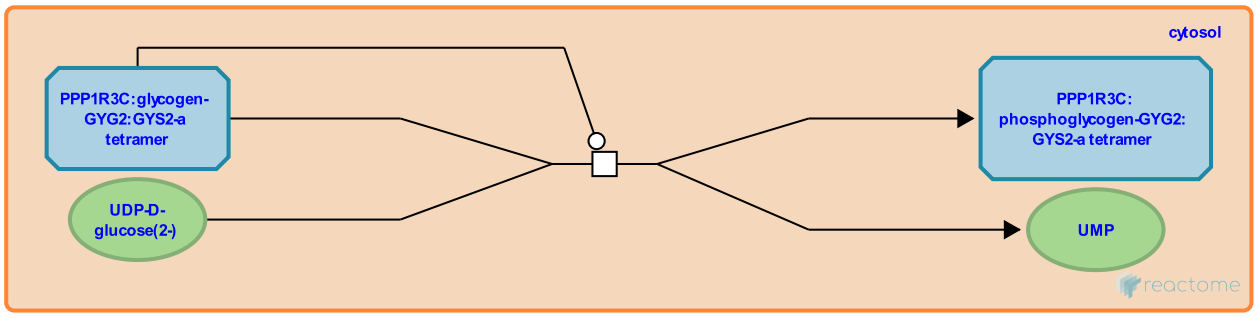
GYS2 catalyzes the incorporation of phosphoglucose into glycogen-GYG2 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3780994

Type: transition

Compartments: cytosol



Glycogen synthase 2 (GYS2) catalyzes the incorporation of phosphoglucose into the glycogen-GYG1 molecules with which it is associated in a cytosolic glycogen granule. This reaction occurs at a low rate, yielding approximately one molecule of glucose phosphorylated at its C2, C3, or C6 positions incorporated into a growing glycogen polymer per ten thousand glucose molecules incorporated (DePaoli-Roach et al. 2015; Irimia et al. 2015; Nitschke et al. 2013; Tagliabracci et al. 2011). The function of these small amounts of phosphoglucose in normal glycogen remains to be established. This reaction has been characterized in muscle cells, where it is catalyzed by the homologous GYS1 enzyme. The occurrence of the reaction in liver, catalyzed by GYS2, can be inferred from the fact that in the absence of the enzyme EMP2A (laforin) that removes these phosphate groups, abnormally phosphorylated glycogen accumulates in both tissues (Worby et al. 2008).

Preceded by: PPP1R3C binds to glycogen:GYG2:GYS2

Followed by: EPM2A dimer binds PPP1R3C:phosphoglycogen-GYG2 complex

Literature references

Ishihara, M., Segvich, DM., Heiss, C., Roach, PJ., Contreras, CJ., Azadi, P. et al. (2015). Glycogen phosphomonoester distribution in mouse models of the progressive myoclonic epilepsy, Lafora disease. *J. Biol. Chem., 290*, 841-50. ↗

Gentry, MS., Worby, CA., Dixon, JE. (2008). Malin decreases glycogen accumulation by promoting the degradation of protein targeting to glycogen (PTG). *J. Biol. Chem., 283*, 4069-76. ↗

Zhao, X., Schmieder, P., Wang, P., Wang, T., Awrey, DE., Girard, JM. et al. (2013). Hyperphosphorylation of glucosyl C6 carbons and altered structure of glycogen in the neurodegenerative epilepsy Lafora disease. *Cell Metab., 17*, 756-67. ↗

Ishihara, M., Hurley, TD., Glushka, J., Heiss, C., Karthik, C., Roach, PJ. et al. (2011). Phosphate incorporation during glycogen synthesis and Lafora disease. *Cell Metab., 13*, 274-82. ↗

Segvich, DM., Meyer, CM., Roach, PJ., Irimia, JM., Tagliabracci, VS., DePaoli-Roach, AA. (2015). Muscle Glycogen Remodeling and Glycogen Phosphate Metabolism following Exhaustive Exercise of Wild Type and Laforin Knockout Mice. *J. Biol. Chem., 290*, 22686-98. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.

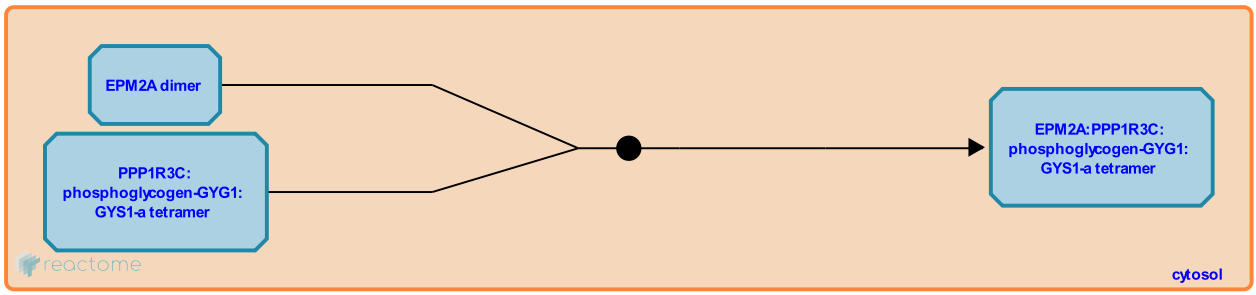
EPM2A dimer binds PPP1R3C:phosphoglycogen-GYG1 complex ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3781001

Type: binding

Compartments: cytosol



EPM2A (laforin) dimer binds to the PPP1R3C:phosphoglycogen-GYG1 (glycogenin 1) complex, probably through interactions with the PPP1R3C (PTG) and glycogen moieties of the complex (Worby et al. 2008).

Preceded by: GYS1 catalyzes the incorporation of phosphoglucose into glycogen-GYG1

Followed by: EPM2A dimer dephosphorylates phosphoglycogen-GYG1

Literature references

Gentry, MS., Worby, CA., Dixon, JE. (2008). Malin decreases glycogen accumulation by promoting the degradation of protein targeting to glycogen (PTG). *J. Biol. Chem., 283*, 4069-76. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.

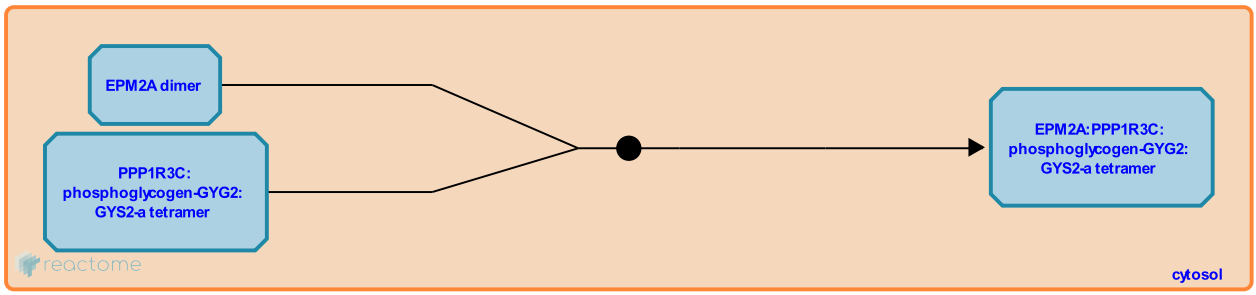
EPM2A dimer binds PPP1R3C:phosphoglycogen-GYG2 complex ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3781021

Type: binding

Compartments: cytosol



EPM2A (laforin) dimer binds to the PPP1R3C:phosphoglycogen-GYG2 (glycogenin 2) complex, probably through interactions with the PPP1R3C (PTG) and glycogen moieties of the complex (Worby et al. 2008). This reaction is inferred from the properties of the better studied muscle glycogen particles containing GYG1 (glycogenin 1), and from the fact that in the absence of EMP2A (laforin) function, liver glycogen particles become abnormal in the same way as do muscle particles.

Preceded by: GYS2 catalyzes the incorporation of phosphoglucose into glycogen-GYG2

Followed by: EPM2A dimer dephosphorylates phosphoglycogen-GYG2

Literature references

Gentry, MS., Worby, CA., Dixon, JE. (2008). Malin decreases glycogen accumulation by promoting the degradation of protein targeting to glycogen (PTG). *J. Biol. Chem., 283*, 4069-76. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.

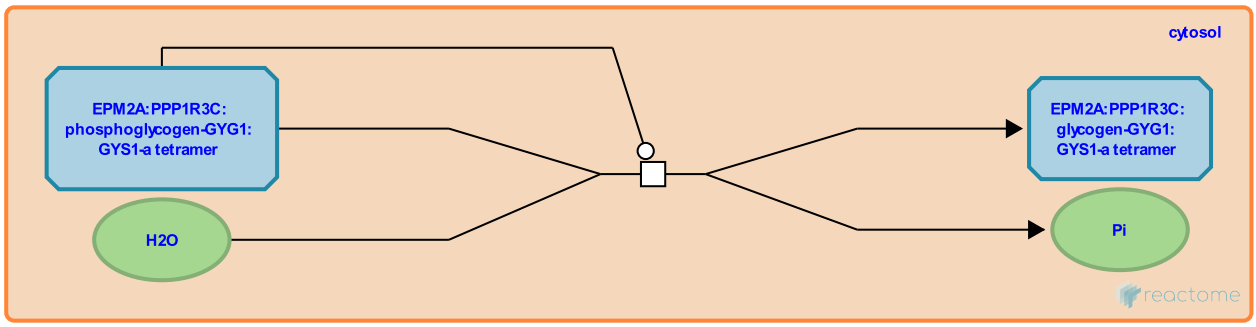
EPM2A dimer dephosphorylates phosphoglycogen-GYG1 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3781018

Type: transition

Compartments: cytosol



EPM2A (laforin), associated with PPP1R3C (protein phosphatase 1 regulatory subunit 3C, PTG) and phosphoglycogen-GYG1 in a cytosolic glycogen particle, catalyzes the dephosphorylation of phosphoglycogen (Tagliabracci et al. 2007). The catalytically active form of EPM2A has been shown to be a homodimer (Raththagala et al. 2015; Sankhala et al. 2015).

Preceded by: EPM2A dimer binds PPP1R3C:phosphoglycogen-GYG1 complex

Followed by: NHLRC1 mediated ubiquitination of EPM2A and PPP1RC3 associated with glycogen-GYG1

Literature references

Parker, MW., Husodo, S., Bridges, TM., Auger, KD., Hellman, LM., Turner, BD. et al. (2015). Structural mechanism of laforin function in glycogen dephosphorylation and lafora disease. *Mol. Cell, 57*, 261-72. ↗

Girard, JM., Roach, PJ., Delgado-Escueta, AV., Tagliabracci, VS., Zhao, X., Skurat, AV. et al. (2007). Laforin is a glycogen phosphatase, deficiency of which leads to elevated phosphorylation of glycogen in vivo. *Proc. Natl. Acad. Sci. U.S.A., 104*, 19262-6. ↗

Cingolani, G., Sankhala, RS., Nitschke, F., Ho, L., Minassian, BA., Koksal, AC. (2015). Dimeric quaternary structure of human laforin. *J. Biol. Chem., 290*, 4552-9. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.

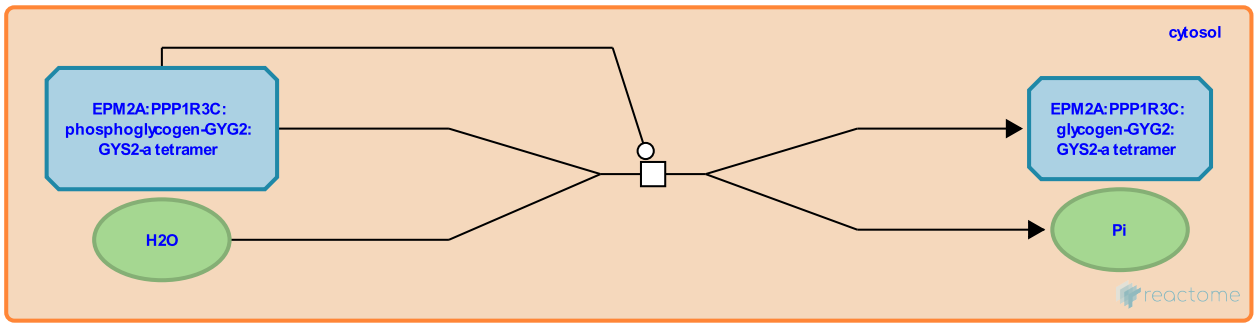
EPM2A dimer dephosphorylates phosphoglycogen-GYG2 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3781011

Type: transition

Compartments: cytosol



EPM2A (laforin), associated with PPP1R3C (protein phosphatase 1 regulatory subunit 3C, PTG) and phosphoglycogen-GYG2 in a cytosolic glycogen particle, catalyzes the dephosphorylation of phosphoglycogen (Tagliabracci et al. 2007). This reaction is inferred from the activity of EPM2A on phosphoglycogen-GYG1, and from the fact that in the absence of normal EPM2A activity, abnormally phosphorylated forms of both glycogen-GYG1 and glycogen-GYG2 accumulate in cells. The catalytically active form of EPM2A has been shown to be a homodimer (Raththagala et al. 2015; Sankhala et al. 2015).

Preceded by: EPM2A dimer binds PPP1R3C:phosphoglycogen-GYG2 complex

Followed by: NHLRC1 mediated ubiquitination of EPM2A (laforin) and PPP1RC3 (PTG) associated with glycogen-GYG2

Literature references

Parker, MW., Husodo, S., Bridges, TM., Auger, KD., Hellman, LM., Turner, BD. et al. (2015). Structural mechanism of laforin function in glycogen dephosphorylation and lafora disease. *Mol. Cell, 57*, 261-72. ↗

Girard, JM., Roach, PJ., Delgado-Escueta, AV., Tagliabracci, VS., Zhao, X., Skurat, AV. et al. (2007). Laforin is a glycogen phosphatase, deficiency of which leads to elevated phosphorylation of glycogen in vivo. *Proc. Natl. Acad. Sci. U.S.A., 104*, 19262-6. ↗

Cingolani, G., Sankhala, RS., Nitschke, F., Ho, L., Minassian, BA., Koksal, AC. (2015). Dimeric quaternary structure of human laforin. *J. Biol. Chem., 290*, 4552-9. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.

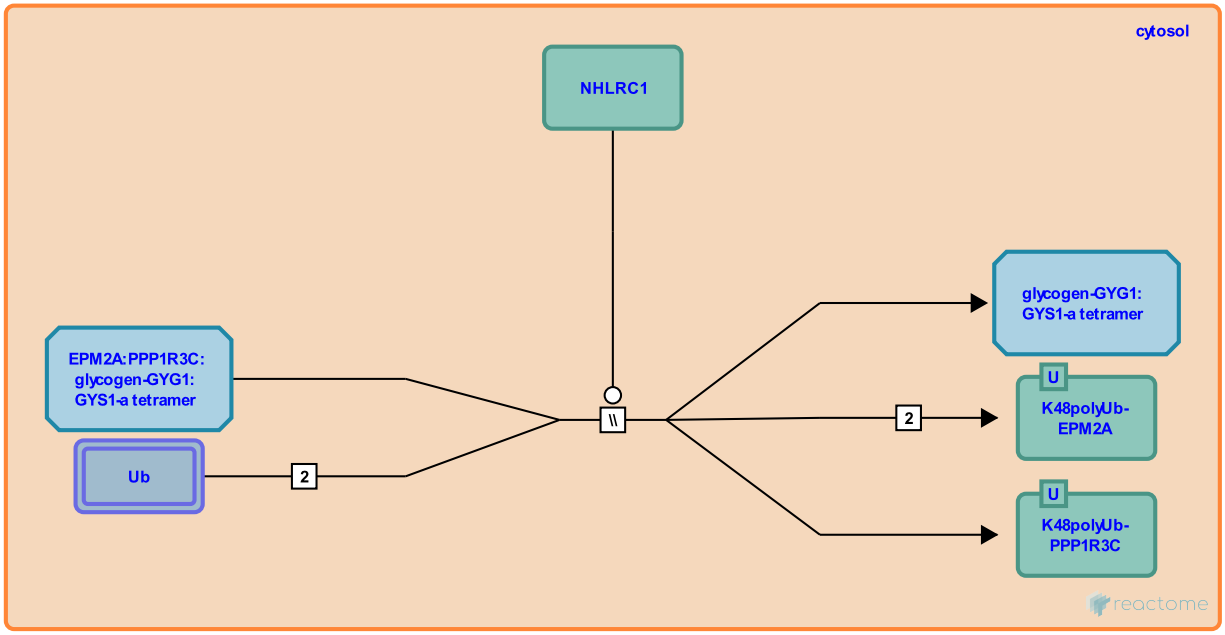
NHLRC1 mediated ubiquitination of EPM2A and PPP1RC3 associated with glycogen-GYG1 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3781009

Type: omitted

Compartments: cytosol



NHLRC1 (malin) associates with the glycogen particle where it functions as a ubiquitin E3 ligase to mediate the polyubiquitination of EPM2A (laforin) and PPP1R3C (PTG). The two polyubiquitinated proteins are targeted for proteasome-mediated degradation, leaving a glycogen-GYG1 particle associated with GYS1 (Gentry et al. 2005, Worby et al. 2008). In NHLRC1 knockout mice, PPP1R3C levels are unchanged, rather than increased, suggesting that NHLRC1 does not target PPP1R3C for degradation. However, EPM2A protein levels are increased in this knockout consistent with NHLRC1's proposed role (DePaoli-Roach et al. 2010).

Preceded by: EPM2A dimer dephosphorylates phosphoglycogen-GYG1

Literature references

Gentry, MS., Worby, CA., Dixon, JE. (2005). Insights into Lafora disease: malin is an E3 ubiquitin ligase that ubiquitinates and promotes the degradation of laforin. *Proc. Natl. Acad. Sci. U.S.A., 102*, 8501-6. ↗

Gentry, MS., Worby, CA., Dixon, JE. (2008). Malin decreases glycogen accumulation by promoting the degradation of protein targeting to glycogen (PTG). *J. Biol. Chem., 283*, 4069-76. ↗

Segvich, DM., Meyer, CM., Roach, PJ., Irimia, JM., Tagliabracci, VS., DePaoli-Roach, AA. (2010). Genetic depletion of the malin E3 ubiquitin ligase in mice leads to lafora bodies and the accumulation of insoluble laforin. *J. Biol. Chem., 285*, 25372-81. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.
2015-08-17	Edited	D'Eustachio, P.

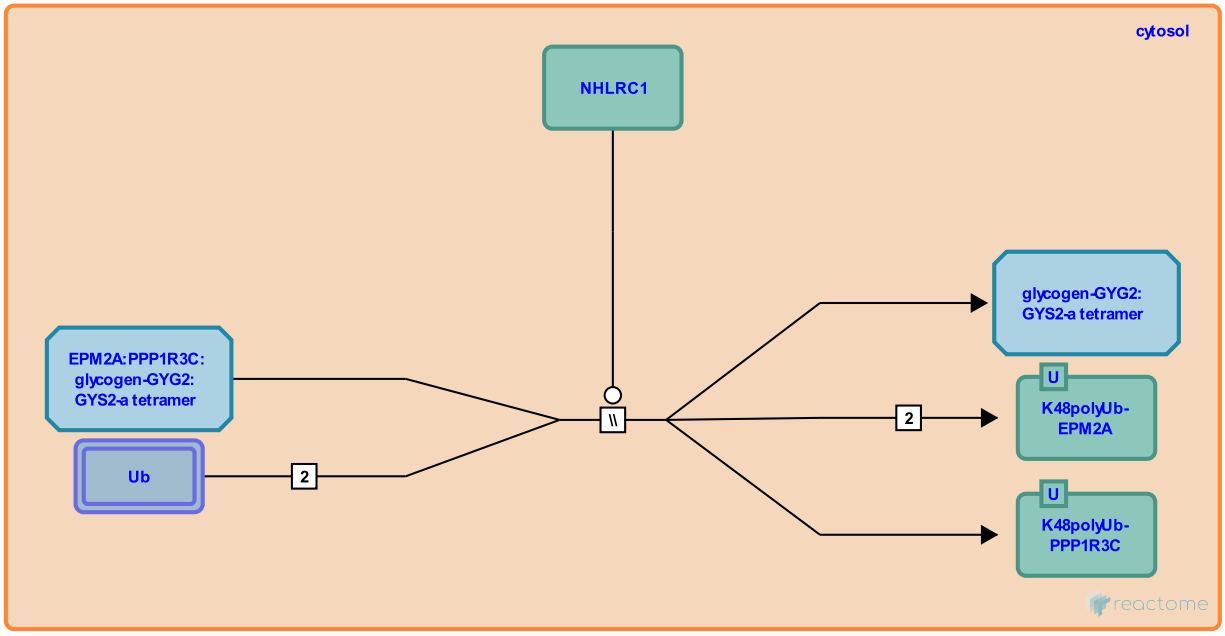
NHLRC1 mediated ubiquitination of EPM2A (laforin) and PPP1RC3 (PTG) associated with glycogen-GYG2 ↗

Location: Glycogen synthesis

Stable identifier: R-HSA-3780995

Type: omitted

Compartments: cytosol



NHLRC1 (malin) associates with the glycogen particle where it functions as a ubiquitin E3 ligase to mediate the polyubiquitination of EPM2A (laforin) and PPP1R3C (protein phosphatase 1 regulatory subunit 3C, PTG). The two polyubiquitinated proteins are targeted for proteasome-mediated degradation, leaving a glycogen-GYG2 particle associated with glycogen synthase 2 GYS2 (Gentry et al. 2005, Worby et al. 2008). In NHLRC1 knockout mice, PPP1R3C levels are unchanged, rather than increased, suggesting that NHLRC1 does not target PPP1R3C for degradation. However, EPM2A protein levels are increased in this knockout consistent with NHLRC1's proposed role. (DePaoli-Roach et al. 2010). This process is inferred from studies of muscle glycogen and from the fact that defects in either EPM2A or NHLRC1 lead to formation of similar aberrant glycogen particles in both tissues.

Preceded by: EPM2A dimer dephosphorylates phosphoglycogen-GYG2

Literature references

Gentry, MS., Worby, CA., Dixon, JE. (2005). Insights into Lafora disease: malin is an E3 ubiquitin ligase that ubiquitinates and promotes the degradation of laforin. *Proc. Natl. Acad. Sci. U.S.A., 102*, 8501-6. ↗

Gentry, MS., Worby, CA., Dixon, JE. (2008). Malin decreases glycogen accumulation by promoting the degradation of protein targeting to glycogen (PTG). *J. Biol. Chem., 283*, 4069-76. ↗

Segvich, DM., Meyer, CM., Roach, PJ., Irimia, JM., Tagliabracci, VS., DePaoli-Roach, AA. (2010). Genetic depletion of the malin E3 ubiquitin ligase in mice leads to lafora bodies and the accumulation of insoluble laforin. *J. Biol. Chem., 285*, 25372-81. ↗

Editions

2013-07-19	Authored	D'Eustachio, P.
2013-07-26	Reviewed	Jassal, B.
2014-02-19	Reviewed	Pederson, B.
2015-08-17	Edited	D'Eustachio, P.

Table of Contents