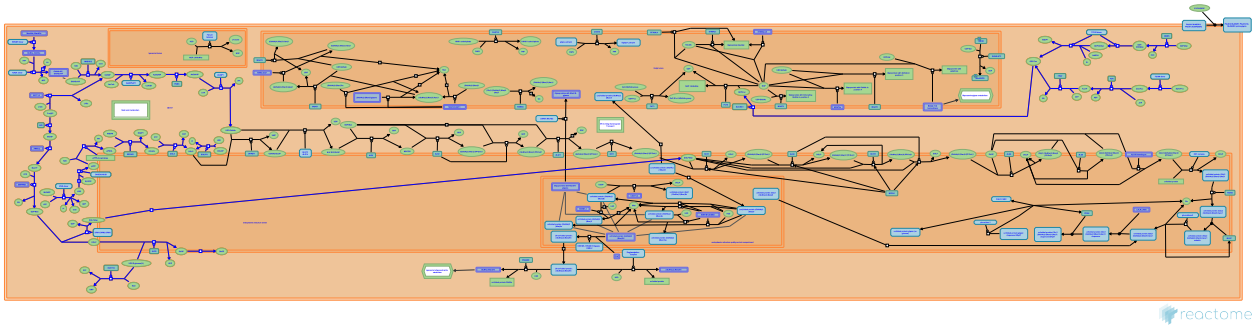
Synthesis of substrates in N-glycan biosynthesis



D'Eustachio, P., Dall'Olio, GM., Gagneux, P., Jassal, B., Medrano, JF., Wickramasinghe, S.

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

06/05/2024

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. ↗

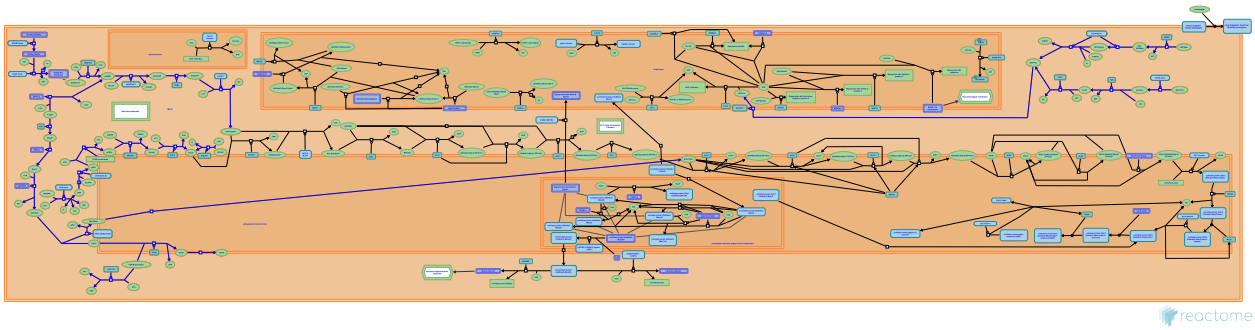
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 8 pathways (see Table of Contents)

Synthesis of substrates in N-glycan biosynthesis ↗

Stable identifier: R-HSA-446219



Reactions for the synthesis of the small nucleotide-linked sugar substrates that are used in the synthesis of the N-glycan precursor and in the later steps of glycosylation are annotated here.
All these nucleotide-linked sugar donors are synthesized in the cytosol; however, to participate in the later reactions of N-glycan precursor biosynthesis (when the glycan is oriented toward the lumen of the endoplasmic reticulum (ER)), these substrates must be attached to a dolichyl-phosphate molecule and then flipped toward the luminal side of the ER, through a mechanism which is still not known but which involves a different protein than the one that mediates the flipping of the LLO itself (Sanyal et al. 2008). Two of the genes encoding enzymes involved in these reactions, MPI and PMM2, are known to be associated with Congenital Disorders of Glycosylation (CDG) diseases of type I. Of these, CDG-Ia, associated with defects in PMM2, is the most frequent CDG disease reported.

Literature references

Sanyal, S., Menon, AK., Frank, CG. (2008). Distinct flippases translocate glycerophospholipids and oligosaccharide diphosphate dolichols across the endoplasmic reticulum. *Biochemistry, 47*, 7937-46. ↗

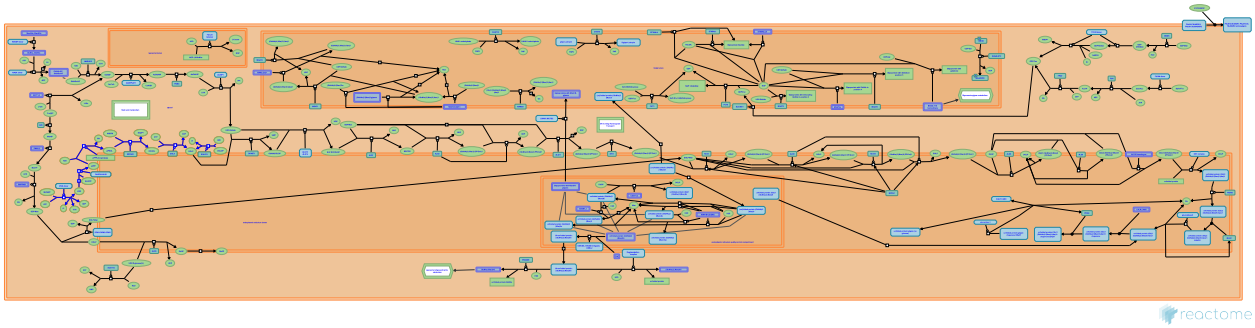
Editions

2009-11-10	Authored	Dall'Olio, GM.
2009-11-10	Edited	Jassal, B.
2010-04-16	Reviewed	Gagneux, P.

Synthesis of Dolichyl-phosphate ↗

Location: Synthesis of substrates in N-glycan biosythesis

Stable identifier: R-HSA-446199



Dolichol is a polyisoprenol lipid comprised of five-carbon isoprene units linked linearly in a head-to-tail fashion. Almost all eukaryotic membranes contain dolichol and its phosphorylated form is used in the N-glycosylation of proteins where it is used as an anchor for the N-glycan sugar to the ER membrane, and as an initiation point for the synthesis. Dolichol biosynthesis occurs on the cytoplasmic face of the ER membrane, which is where N-glycosylation occurs too, so is perfectly placed to serve as a substrate for this process. Dolichyl phosphate can be obtained either from direct phosphorylation of dolichol, formed in a series of reactions from mevalonate 5-pyrophosphate, or a salvage reaction by de-phosphorylation of dolichyl diphosphate, released at the end of N-glycan biosynthesis (Cantagrel & Lefeber 2011).

Literature references

Lefeber, DJ., Cantagrel, V. (2011). From glycosylation disorders to dolichol biosynthesis defects: a new class of metabolic diseases. *J. Inherit. Metab. Dis., 34*, 859-67. ↗

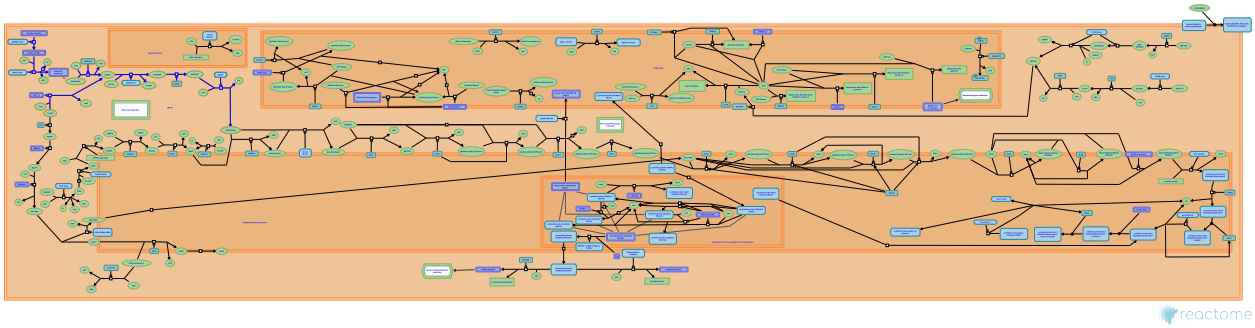
Editions

2009-11-10	Authored	Dall'Olio, GM.
2009-11-10	Edited	Jassal, B.
2010-04-16	Reviewed	Gagneux, P.

Synthesis of UDP-N-acetyl-glucosamine ↗

Location: Synthesis of substrates in N-glycan biosythesis

Stable identifier: R-HSA-446210



UDP-acetylglucosamine acts as a donor for the first two steps of the N-glycan precursor biosynthesis pathway, and is later used as a substrate for further modifications after the precursor has been attached to the protein. It is synthesized from fructose 6-phosphate, glutamine, acetyl-CoA, and UTP in four steps.

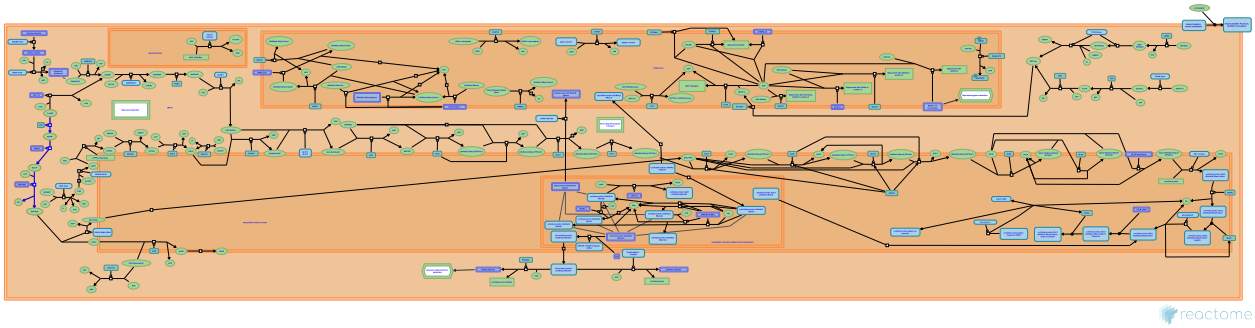
Editions

2009-11-10	Authored	Dall'Olio, GM.
2009-11-10	Edited	Jassal, B.
2010-04-16	Reviewed	Gagneux, P.

Synthesis of GDP-mannose ↗

Location: Synthesis of substrates in N-glycan biosythesis

Stable identifier: R-HSA-446205



GDP-mannose is the mannose donor for the first 5 mannose addition reactions in the N-glycan precursor synthesis, and also for the synthesis of Dolichyl-phosphate-mannose involved in other mannose transfer reactions. It is synthesized from fructose 6-phosphate and GTP in three steps.

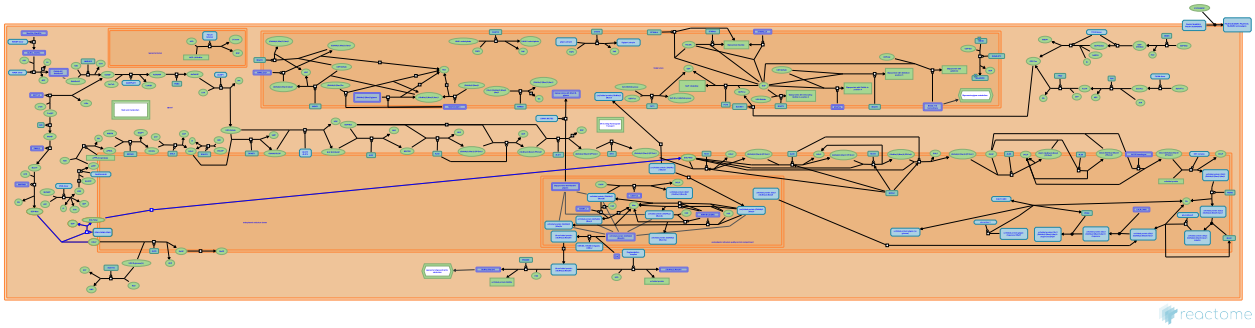
Editions

2009-11-10	Authored	Dall'Olio, GM.
2009-11-10	Edited	Jassal, B.
2010-04-16	Reviewed	Gagneux, P.

Synthesis of dolichyl-phosphate mannose ↗

Location: Synthesis of substrates in N-glycan biosythesis

Stable identifier: R-HSA-162699



Dolichyl-phosphate-mannose (DPM, DOLPman) is the donor of mannose groups in the synthesis of the dolichyl pyrophosphate-linked precursor oligosaccharide in asparagine-linked glycosylation, in the synthesis of the glycosyl phosphatidylinositol (GPI) anchor precursor, in protein O-mannosylation and in protein C-mannosylation. Its synthesis proceeds in two steps. First, cytosolic GDP-mannose reacts with dolichyl phosphate exposed on the cytosolic face of the endoplasmic reticulum membrane to form DPM with its mannose moiety oriented toward the cytosol. The DPM molecule then flips in the endoplasmic reticulum membrane, so that its mannose moiety is in the endoplasmic reticulum lumen, accessible to the enzymes that catalyze its transfer to growing glycolipids and glycoproteins (Kinoshita and Inoue, 2000; Maeda et al, 2000).

Literature references

Kinoshita, T., Kangawa, K., Hino, J., Tanaka, S., Maeda, Y. (2000). Human dolichol-phosphate-mannose synthase consists of three subunits, DPM1, DPM2 and DPM3. *EMBO J, 19*, 2475-82. ↗

Kinoshita, T., Inoue, N. (2000). Dissecting and manipulating the pathway for glycosylphosphatidylinositol-anchor biosynthesis. *Curr Opin Chem Biol, 4*, 632-8. ↗

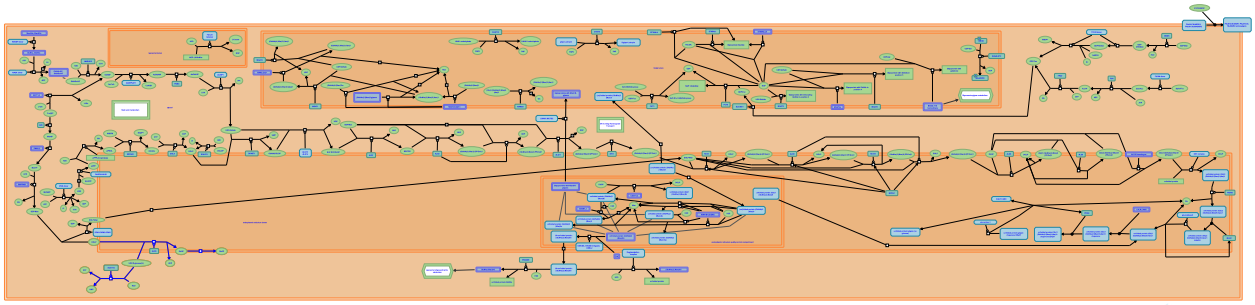
Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-04-16	Reviewed	Gagneux, P.
2024-03-06	Edited	D'Eustachio, P.

Synthesis of dolichyl-phosphate-glucose ↗

Location: Synthesis of substrates in N-glycan biosythesis

Stable identifier: R-HSA-480985



Dolichyl-phosphate-glucose functions as a donor of glucose groups in reactions including three steps of N-glycan precursor biosynthesis. Dolichyl-phosphate-glucose itself is synthesized from UDP-glucose and dolichol phosphate on the cytosolic face of the endoplasmic reticulum membrane, then flipped to the luminal surface of that membrane.

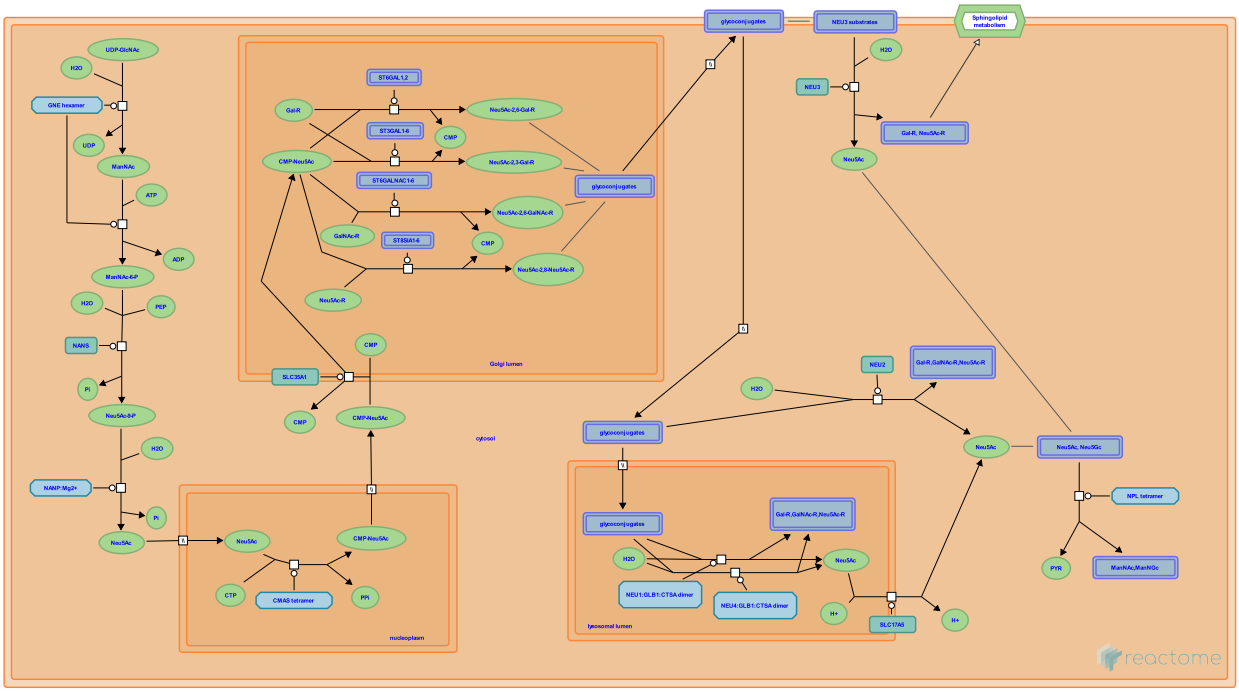
Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-01-27	Edited	Jassal, B.
2010-04-16	Reviewed	Gagneux, P.

Sialic acid metabolism ↗

Location: Synthesis of substrates in N-glycan biosythesis

Stable identifier: R-HSA-4085001



Sialic acids are a family of 9 carbon alpha-keto acids that are usually present in the non reducing terminal of glycoconjugates on the cell surface of eukaryotic cells. These sialylated conjugates play important roles in cell recognition and signaling, neuronal development, cancer metastasis and bacterial or viral infection. More than 50 forms of sialic acid are found in nature, the most abundant being N-acetylneuraminic acid (Neu5Ac, N-acetylneuraminate) (Li & Chen 2012, Wickramasinghe & Medrano 2011). The steps below describe the biosynthesis, transport, utilization and degradation of Neu5Ac in humans.

Literature references

Li, Y., Chen, X. (2012). Sialic acid metabolism and sialyltransferases: natural functions and applications. *Appl. Microbiol. Biotechnol., 94*, 887-905. ↗

Wickramasinghe, S., Medrano, JF. (2011). Primer on genes encoding enzymes in sialic acid metabolism in mammals. *Biochimie, 93*, 1641-6. ↗

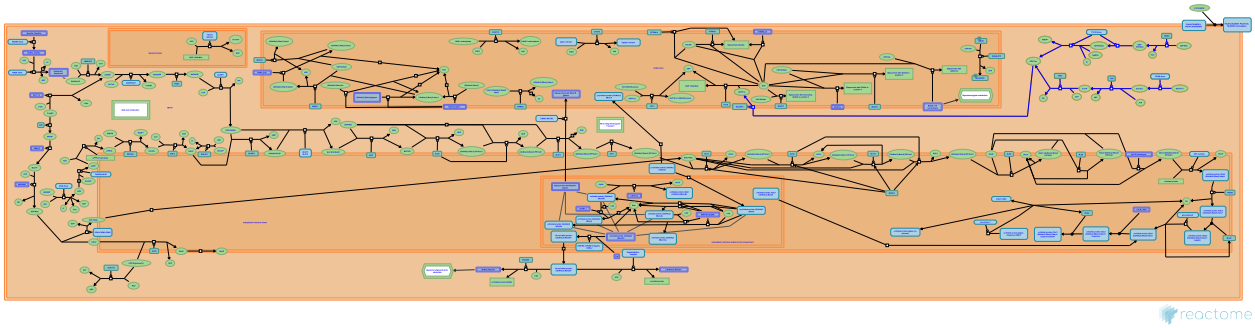
Editions

2013-08-01	Authored, Edited	Jassal, B.
2014-01-08	Reviewed	Wickramasinghe, S., Medrano, JF.

GDP-fucose biosynthesis ↗

Location: Synthesis of substrates in N-glycan biosythesis

Stable identifier: R-HSA-6787639



Fucose-containing glycans play important roles in immunity and signalling. Fucosylated glycans are created by fucosyltransferases, which require the high-energy donor substrate GDP-fucose. Two pathways for the synthesis of GDP-fucose exist in mammalian cells; the GDP-mannose-dependent de novo pathway provides the majority of GDP-fucose whereas a minor contribution comes from the free fucose-dependent salvage pathway (Becker & Lowe 2003).

Literature references

Lowe, JB., Becker, DJ. (2003). Fucose: biosynthesis and biological function in mammals. *Glycobiology, 13*, 41R-53R. ↗

Editions

2015-07-15	Authored, Edited	Jassal, B.
2015-09-14	Reviewed	D'Eustachio, P.

Table of Contents