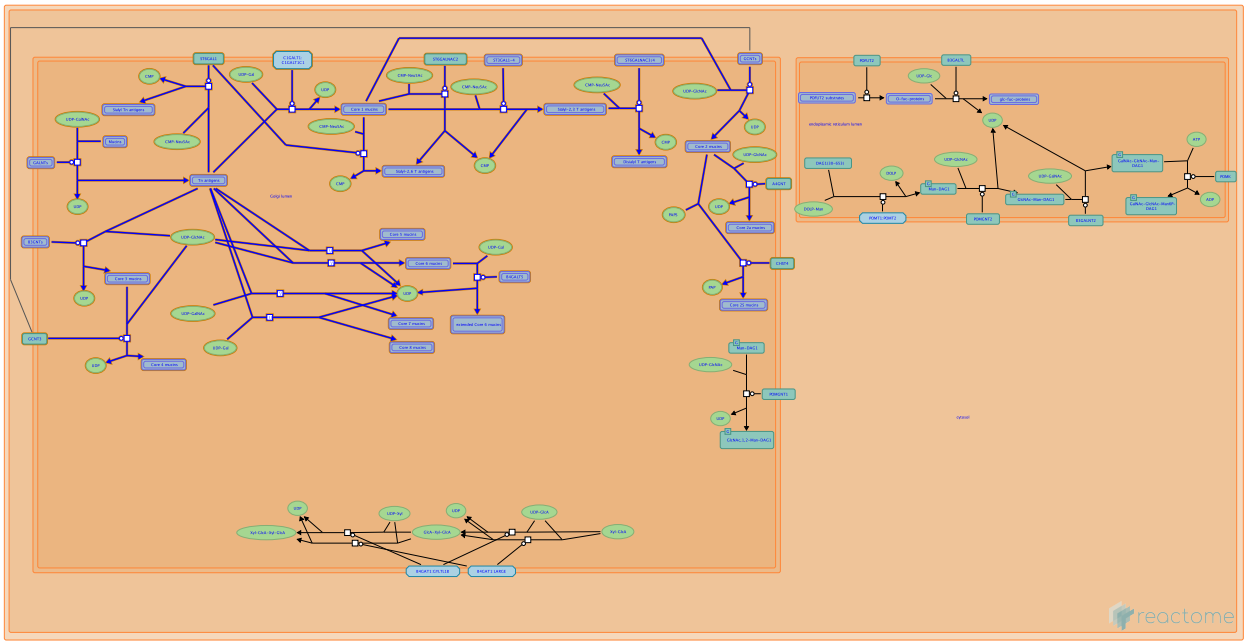
O-linked glycosylation of mucins



D'Eustachio, P., Ferrer, A., Jassal, B.

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

24/08/2021

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. ↗

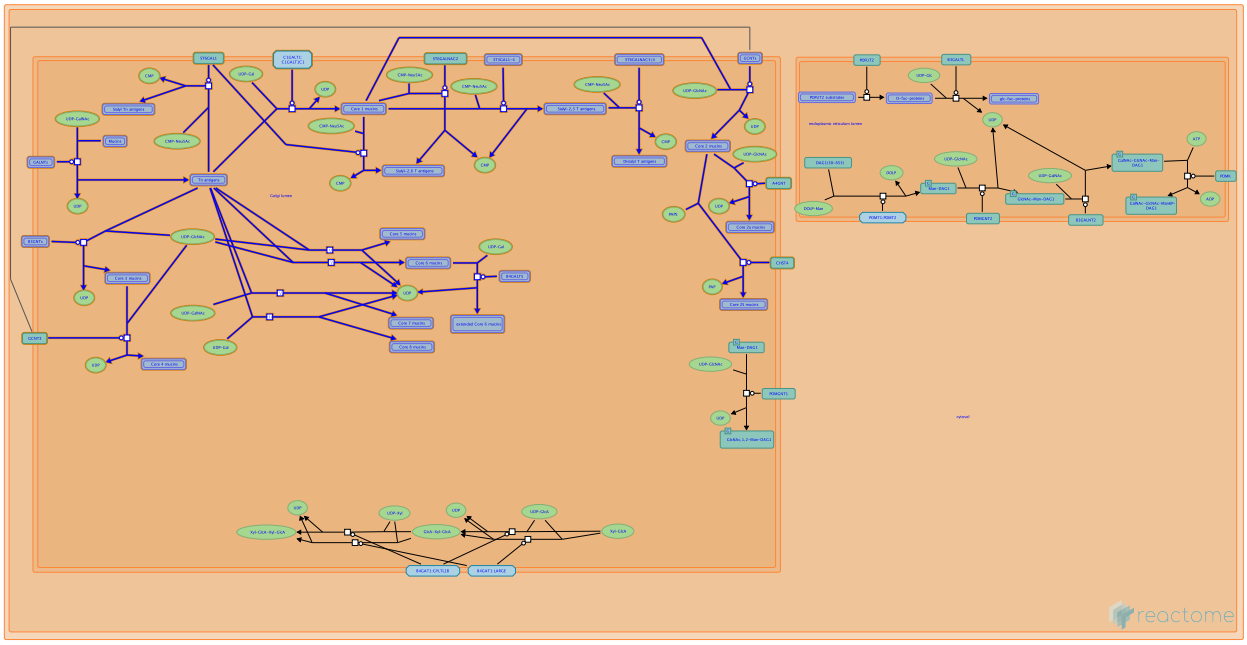
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

O-linked glycosylation of mucins ↗

Stable identifier: R-HSA-913709



Mucins are a family of high molecular weight, heavily glycosylated proteins (glycoconjugates) produced by epithelial tissues in most metazoa. Mucins' key characteristic is their ability to form gels; therefore they are a key component in most gel-like secretions, serving functions from lubrication to cell signalling to forming chemical barriers. To date, there are approximately 20 genes that express mucins. Mature mucins are composed of two distinct regions:

(1) The amino- and carboxy-terminal regions are very lightly glycosylated, but rich in cysteines. The cysteine residues participate in establishing disulfide linkages within and among mucin monomers.

(2) A large central region rich in serine, threonine and proline residues called the variable number of tandem repeat (VNTR) region which can become heavily O-glycosylated with hundreds of O-GalNAc glycans.

N-acetyl-galactosamine (GalNAc) is the first glycan to be attached, forming the simplest mucin O-glycan. After this, several different pathways are possible generating "core" structures. Four core structures are commonly formed, several others are possible but infrequent. O-linked glycans are often capped by the addition of a sialic acid residue, terminating the addition of any more O-glycans (Brockhausen et al, 2009; Tarp and Clausen, 2008).

Literature references

Tarp, MA., Clausen, H. (2008). Mucin-type O-glycosylation and its potential use in drug and vaccine development. *Biochim Biophys Acta, 1780*, 546-63. ↗

Brockhausen, I., Schachter, H., Stanley, P., Stanley, P., Varki, A., Cummings, RD. et al. (2009). O-GalNAc Glycans.

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

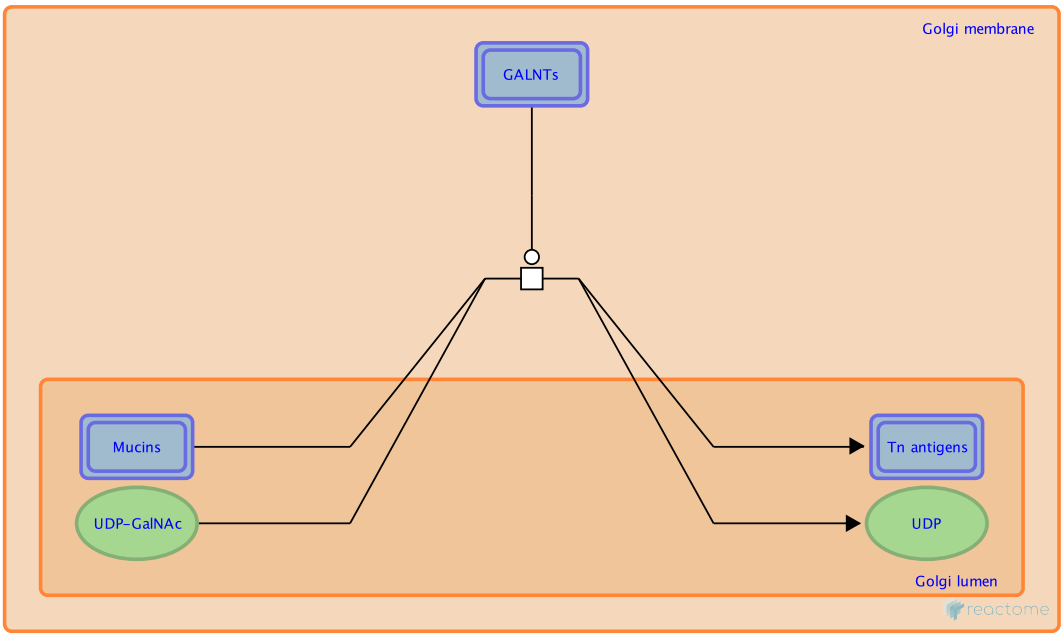
GALNTs transfer GalNAc from UDP-GalNAc to mucins to form Tn antigens ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-913675

Type: transition

Compartments: Golgi membrane, Golgi lumen



The family of UDP GalNAc:polypeptide N acetylgalactosaminyltransferases (GalNAc transferases, GALNTs) carry out the addition of N acetylgalactosamine on serine, threonine or possibly tyrosine residues on a wide variety of proteins, and most commonly associated with mucins (Wandall et al. 1997). This reaction takes place in the Golgi apparatus (Rottger et al. 1998). There are 20 known members of the GALNT family, 15 of which have been characterised and 5 candidate members which are thought to belong to this family based on sequence similarity (Bennett et al. 2012). The GALNT-family is classified as belonging to CAZy family GT27.

Followed by: Addition of galactose to the Tn antigen via an alpha-1,3 linkage forms a Core 8 glycoprotein , Addition of GlcNAc to the Tn antigen via an alpha-1,3 linkage forms a Core 5 glycoprotein, Addition of GlcNAc to the Tn antigen forms a Core 3 glycoprotein, Addition of GalNAc to the Tn antigen via an alpha-1,6 linkage forms a Core 7 glycoprotein, Addition of GlcNAc to the Tn antigen via a beta-1,6 linkage forms a Core 6 glycoprotein, C1GALT1 transfers Galactose to the Tn antigen forming Core 1 glycoproteins (T antigens)

Literature references

Wandall, HH., Hassan, H., Mirgorodskaya, E., Kristensen, AK., Roepstorff, P., Bennett, EP. et al. (1997). Substrate specificities of three members of the human UDP-N-acetyl-alpha-D-galactosamine:Polypeptide N-acetylgalactosaminyltransferase family, GalNAc-T1, -T2, and -T3. *J Biol Chem, 272*, 23503-14. ↗

Röttger, S., White, J., Wandall, HH., Olivo, JC., Stark, A., Bennett, EP. et al. (1998). Localization of three human polypeptide GalNAc-transferases in HeLa cells suggests initiation of O-linked glycosylation throughout the Golgi apparatus. *J Cell Sci, 111*, 45-60. ↗

Bennett, EP., Mandel, U., Clausen, H., Gerken, TA., Fritz, TA., Tabak, LA. (2012). Control of mucin-type O-glycosylation: a classification of the polypeptide GalNAc-transferase gene family. *Glycobiology, 22*, 736-56. ↗

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

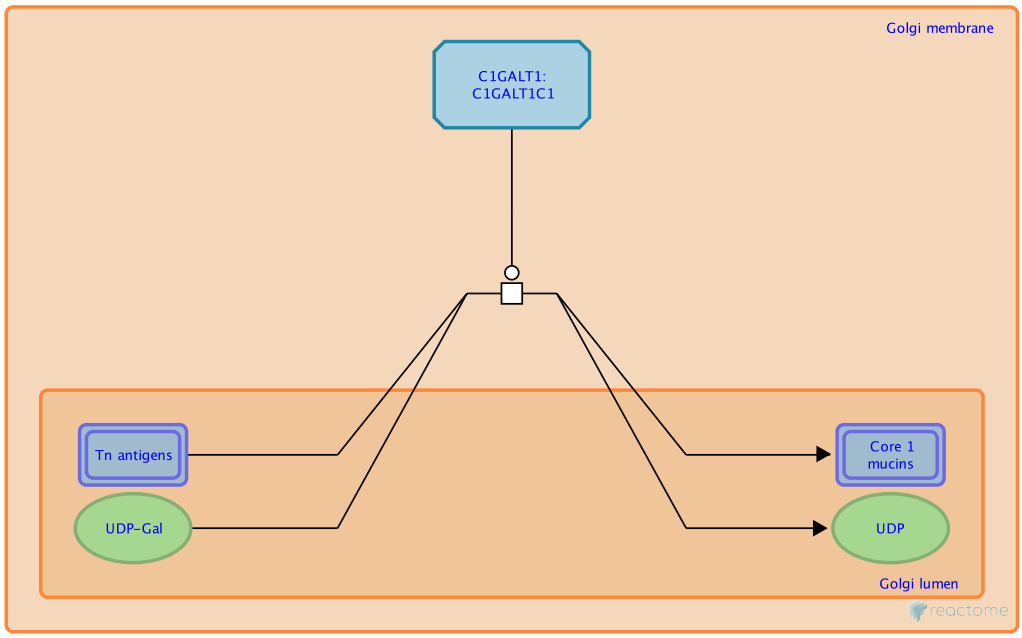
C1GALT1 transfers Galactose to the Tn antigen forming Core 1 glycoproteins (T antigens) ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-1964505

Type: transition

Compartments: Golgi membrane, Golgi lumen



Glycoprotein N acetylgalactosamine 3 beta galactosyltransferase 1 (C1GALT1; MIM:610555) mediates the transfer of Galactose (Gal) from UDP galactose to single O-linked GalNAc residues (Tn antigens) to form Core 1 structures on glycoproteins. C1GALT1 is active when in complex with the molecular chaperone C1GALT1C1 (aka COSMC; MIM:300611) which assists the folding and/or stability of C1GALT1. Defects in C1GALT1C1 causes somatic Tn polyagglutination syndrome (TNPS; MIM:300622), characterised by the polyagglutination of erythrocytes by naturally occurring anti Tn antibodies following exposure of the Tn antigen on their surface. Defects in C1GALT1C1 render C1GALT1 inactive and results in the accumulation of the incompletely glycosylated Tn antigen. The Tn antigen is tumour associated, found in a majority of human carcinomas, and is not normally expressed in peripheral tissues or blood cells (Crew et al. 2008, Ju et al. 2014). C1GALT1 and C1GALT1C1 belong to the CAZy family GT31 (CAZy.org).

Preceded by: GALNTs transfer GalNAc from UDP-GalNAc to mucins to form Tn antigens

Followed by: GCNTs transfer GlcNAc from UDP-GlcNAc to Core 1 mucins

Literature references

Crew, VK., Singleton, BK., Green, C., Parsons, SF., Daniels, G., Anstee, DJ. (2008). New mutations in C1GALT1C1 in individuals with Tn positive phenotype. *Br. J. Haematol., 142*, 657-67. ↗

Ju, T., Aryal, RP., Kudelka, MR., Wang, Y., Cummings, RD. (2014). The Cosmc connection to the Tn antigen in cancer . *Cancer Biomark, 14*, 63-81. ↗

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

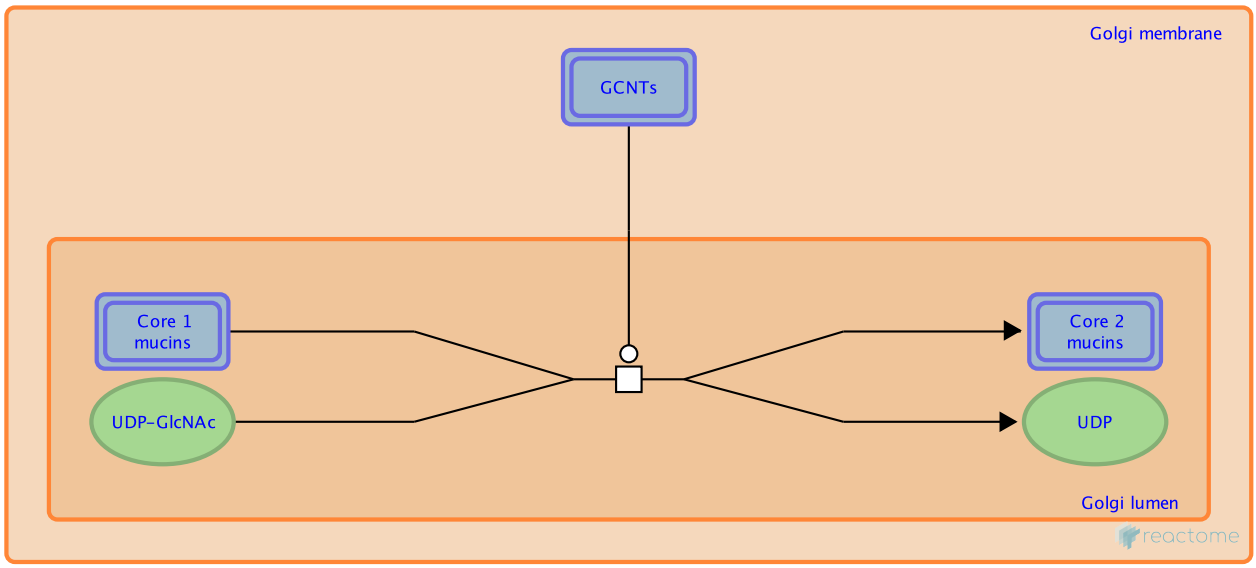
GCNTs transfer GlcNAc from UDP-GlcNAc to Core 1 mucins ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-914012

Type: transition

Compartments: Golgi lumen, Golgi membrane



The human gene GCNT encodes beta-1,6-N-acetylglucosaminyltransferase which mediates core 2 O-glycan branching by the addition of N-acetylgalactosamine, an important step in mucin-type biosynthesis. There are 3 defined members in humans, 1, 3 and 4 (Bierhuizen and Fukuda, 1992; Yeh et al, 1999; Schwientek et al, 2000). Two members (6 and 7) may be part of the family based on sequence similarity.

Preceded by: C1GALT1 transfers Galactose to the Tn antigen forming Core 1 glycoproteins (T antigens)

Followed by: CHST4 transfers SO4(2-) from PAPS to Core 2 mucins

Literature references

Bierhuizen, MF., Fukuda, M. (1992). Expression cloning of a cDNA encoding UDP-GlcNAc:Gal beta 1-3-GalNAc-R (GlcNAc to GalNAc) beta 1-6GlcNAc transferase by gene transfer into CHO cells expressing polyoma large tumor antigen. *Proc Natl Acad Sci U S A, 89*, 9326-330. ↗

Yeh, JC., Ong, E., Fukuda, M. (1999). Molecular cloning and expression of a novel beta-1, 6-N-acetylglucosaminyltransferase that forms core 2, core 4, and I branches. *J Biol Chem, 274*, 3215-21. ↗

Schwientek, T., Yeh, JC., Levery, SB., Keck, B., Merkx, G., van Kessel, AG. et al. (2000). Control of O-glycan branch formation. Molecular cloning and characterization of a novel thymus-associated core 2 beta1, 6-n-acetylglucosaminyltransferase. *J Biol Chem, 275*, 11106-13. ↗

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

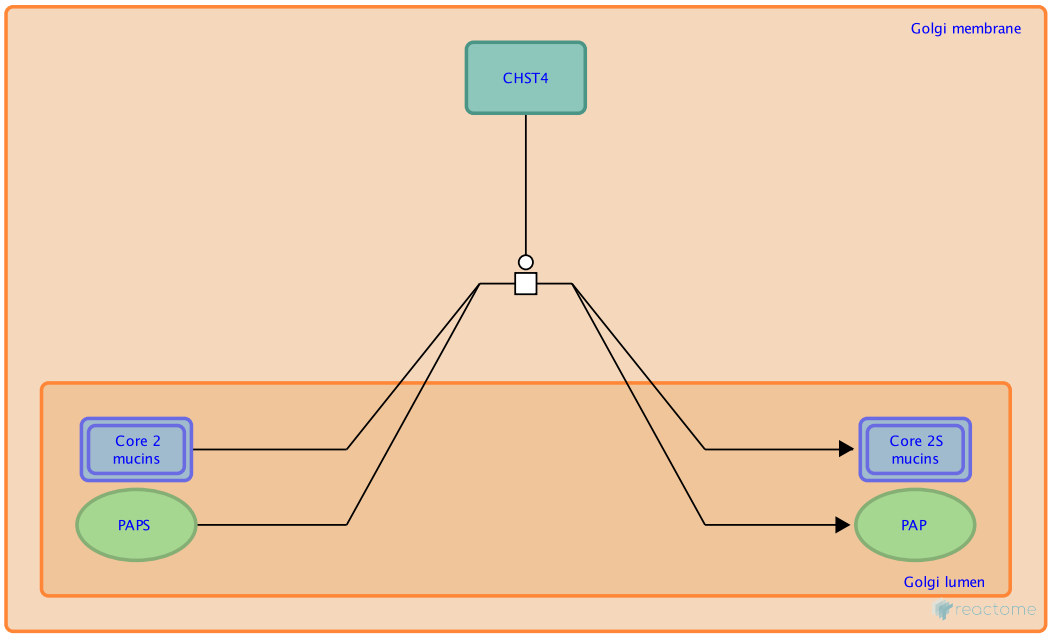
CHST4 transfers SO4(2-) from PAPS to Core 2 mucins ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-6786012

Type: transition

Compartments: Golgi membrane, Golgi lumen



Carbohydrate sulfotransferase 4 (CHST4) transfers sulfate (SO4(2-)) from the high energy donor 3'-phospho-5'-adenylyl sulfate (PAPS) to position 6 of non-reducing N-acetylglucosamine (GlcNAc) residues of mucin-associated glycans that ultimately serve as SELL ligands which are present in high endothelial cells (HEVs) and play a central role in lymphocyte homing at sites of inflammation. CHST4 preferentially sulfates Core 2 mucins (Bistrup et al. 1999). CHST4 is localised to the Golgi membrane (de Graffenried & Bertozzi 2004).

Preceded by: GCNTs transfer GlcNAc from UDP-GlcNAc to Core 1 mucins

Literature references

Bistrup, A., Bhakta, S., Lee, JK., Belov, YY., Gunn, MD., Zuo, FR. et al. (1999). Sulfotransferases of two specificities function in the reconstitution of high endothelial cell ligands for L-selectin. *J. Cell Biol., 145*, 899-910. ↗

de Graffenried, CL., Bertozzi, CR. (2003). Golgi localization of carbohydrate sulfotransferases is a determinant of L-selectin ligand biosynthesis. *J. Biol. Chem., 278*, 40282-95. ↗

Editions

2015-07-03	Authored, Edited	Jassal, B.
2015-09-14	Reviewed	D'Eustachio, P.

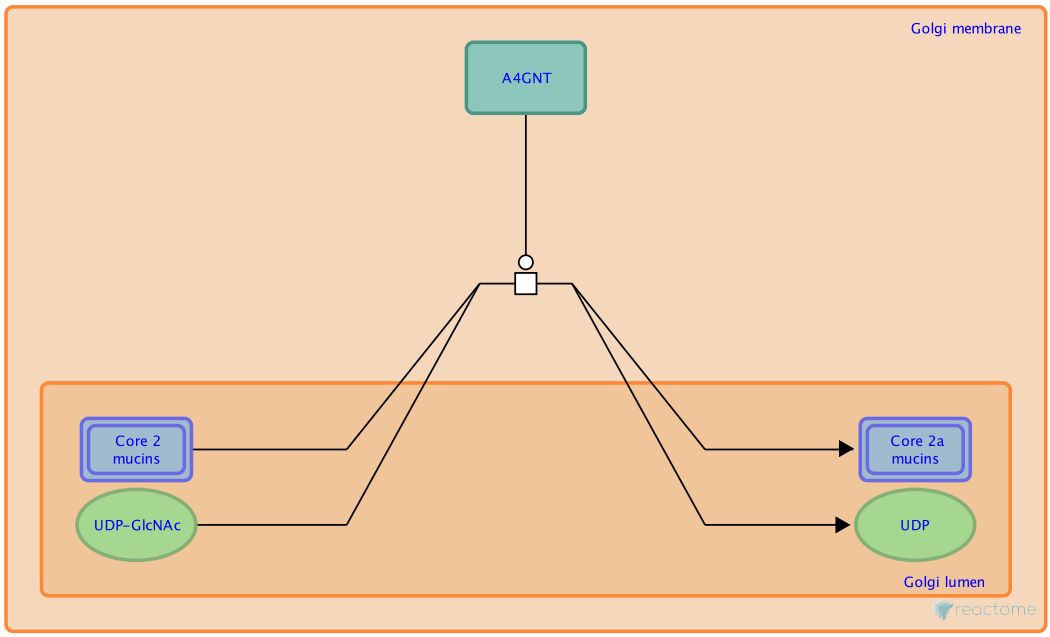
A4GNT transfers GlcNAc to core 2 mucins ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-5694487

Type: transition

Compartments: Golgi membrane, Golgi lumen



Alpha-1,4-N-acetylglucosaminyltransferase (A4GNT) can catalyse the transfer of N-acetylglucosamine (GlcNAc) to core 2 branched mucins, creating an alpha1,4-linkage with beta-Gal residues (arbitrarily named Core 2a mucins) (Nakayama et al. 1999, Zhang et al. 2001).

Literature references

Nakayama, J., Yeh, JC., Misra, AK., Ito, S., Katsuyama, T., Fukuda, M. (1999). Expression cloning of a human alpha1, 4-N-acetylglucosaminyltransferase that forms GlcNAcalpha1-->4Galbeta-->R, a glycan specifically expressed in the gastric gland mucous cell-type mucin. *Proc. Natl. Acad. Sci. U.S.A., 96*, 8991-6. ↗

Zhang, MX., Nakayama, J., Hidaka, E., Kubota, S., Yan, J., Ota, H. et al. (2001). Immunohistochemical demonstration of alpha1,4-N-acetylglucosaminyltransferase that forms GlcNAcalpha1,4Galbeta residues in human gastrointestinal mucosa. *J. Histochem. Cytochem., 49*, 587-96. ↗

Editions

2015-05-21	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

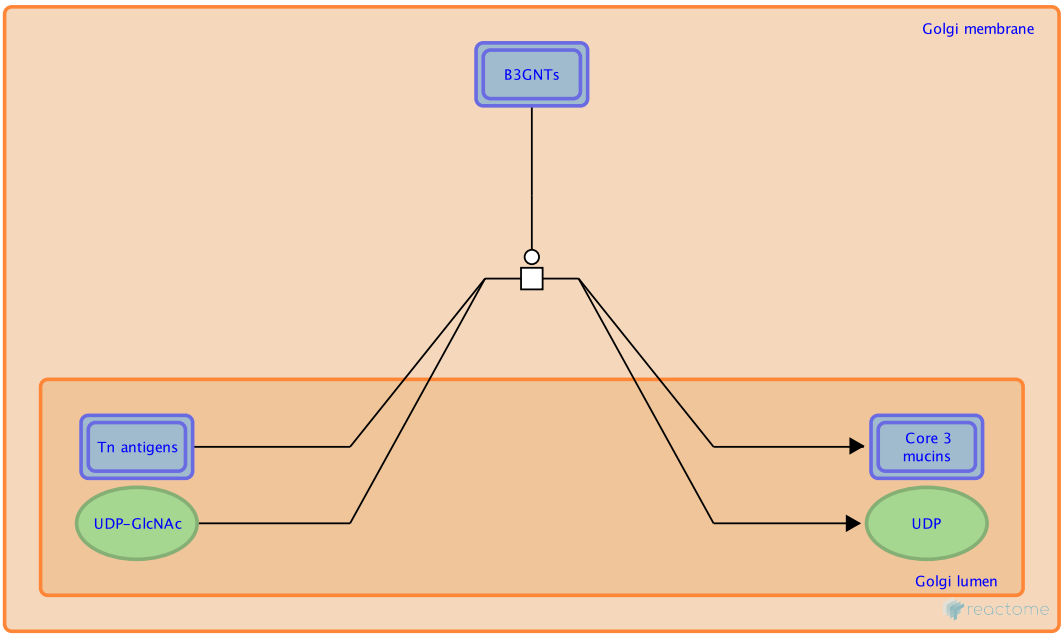
Addition of GlcNAc to the Tn antigen forms a Core 3 glycoprotein ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-914010

Type: transition

Compartments: Golgi membrane, Golgi lumen



The UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase family (B3GNTs) consists of 9 members in humans (Kolbinger et al, 1998; Shiraishi et al, 2001; Togayachi et al, 2001; Iwai et al, 2002; Huang et al, 2004; Ishida et al, 2005; Zheng et al, 2004). They catalyse the addition of N-acetylglucosamine to the T antigen to form the Core 3 glycoprotein (Togayachi et al, 2006). Thie reaction occurs in the Golgi.

Preceded by: GALNTs transfer GalNAc from UDP-GalNAc to mucins to form Tn antigens

Followed by: Addition of GlcNAc to Core 3 forms a Core 4 glycoprotein

Literature references

Togayachi, A., Sato, T., Narimatsu, H. (2006). Comprehensive enzymatic characterization of glycosyltransferases with a beta3GT or beta4GT motif. *Methods Enzymol, 416*, 91-102. ↗

Kolbinger, F., Streiff, MB., Katopodis, AG. (1998). Cloning of a human UDP-galactose:2-acetamido-2-deoxy-D-glucose 3beta-galactosyltransferase catalyzing the formation of type 1 chains. *J Biol Chem, 273*, 433-40. ↗

Shiraishi, N., Natsume, A., Togayachi, A., Endo, T., Akashima, T., Yamada, Y. et al. (2001). Identification and characterization of three novel beta 1,3-N-acetylglucosaminyltransferases structurally related to the beta 1,3-galactosyltransferase family. *J Biol Chem, 276*, 3498-507. ↗

Togayachi, A., Akashima, T., Ookubo, R., Kudo, T., Nishihara, S., Iwasaki, H. et al. (2001). Molecular cloning and characterization of UDP-GlcNAc:lactosylceramide beta 1,3-N-acetylglucosaminyltransferase (beta 3Gn-T5), an essential enzyme for the expression of HNK-1 and Lewis X epitopes on glycolipids. *J Biol Chem, 276*, 22032-40. ↗

Iwai, T., Inaba, N., Naundorf, A., Zhang, Y., Gotoh, M., Iwasaki, H. et al. (2002). Molecular cloning and characterization of a novel UDP-GlcNAc:GalNAc-peptide beta1,3-N-acetylglucosaminyltransferase (beta 3Gn-T6), an enzyme synthesizing the core 3 structure of O-glycans. *J Biol Chem, 277*, 12802-9. ↗

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

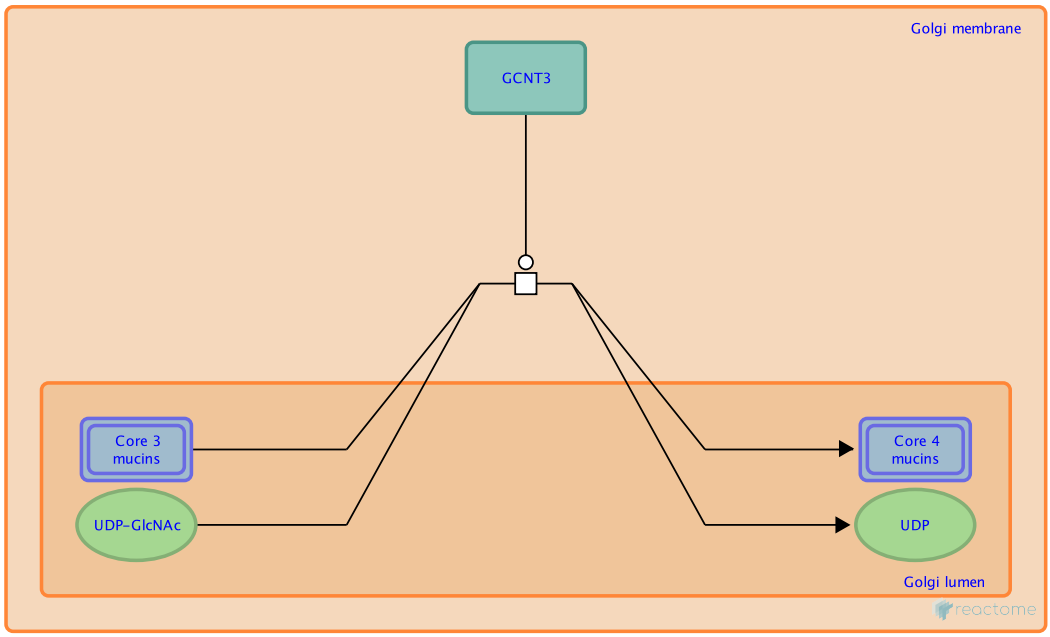
Addition of GlcNAc to Core 3 forms a Core 4 glycoprotein ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-914018

Type: transition

Compartments: Golgi membrane, Golgi lumen



The glycosyltransferase GCNT3 mediates core 2 and core 4 O-glycan branching (Yeh et al, 1999; Schwientek et al, 1999).

Preceded by: Addition of GlcNAc to the Tn antigen forms a Core 3 glycoprotein

Literature references

Yeh, JC., Ong, E., Fukuda, M. (1999). Molecular cloning and expression of a novel beta-1, 6-N-acetylglucosaminyl-transferase that forms core 2, core 4, and I branches. *J Biol Chem, 274*, 3215-21. ↗

Schwientek, T., Nomoto, M., Levery, SB., Merkx, G., van Kessel, AG., Bennett, EP. et al. (1999). Control of O-glycan branch formation. Molecular cloning of human cDNA encoding a novel beta1,6-N-acetylglucosaminyltransferase forming core 2 and core 4. *J Biol Chem, 274*, 4504-12. ↗

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

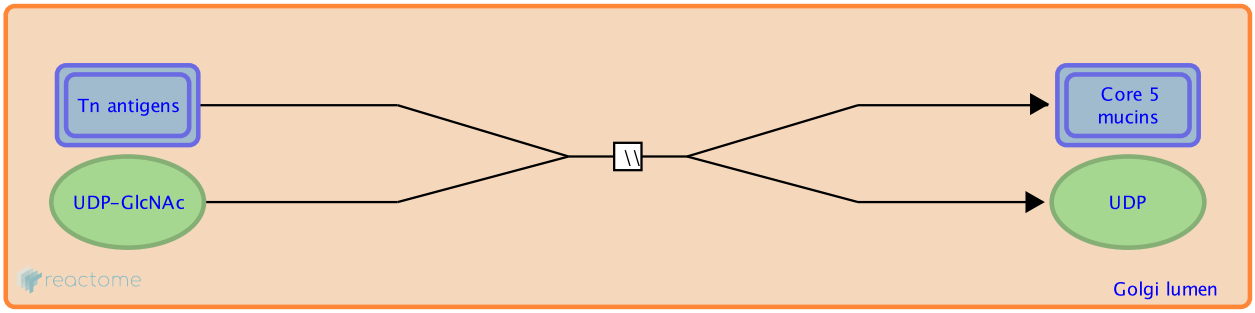
Addition of GlcNAc to the Tn antigen via an alpha-1,3 linkage forms a Core 5 glycoprotein ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-914005

Type: omitted

Compartments: Golgi lumen



An unknown N-acetylglucosaminyltransferase mediates the transfer of GlcNAc to Tn antigens via an alpha-1,3 linkage to create Core 5 mucins (Brockhausen et al. 2009).

Preceded by: GALNTs transfer GalNAc from UDP-GalNAc to mucins to form Tn antigens

Literature references

Brockhausen, I., Schachter, H., Stanley, P. (2009). O-GalNAc Glycans, Essentials of Glycobiology, 2nd edition.

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

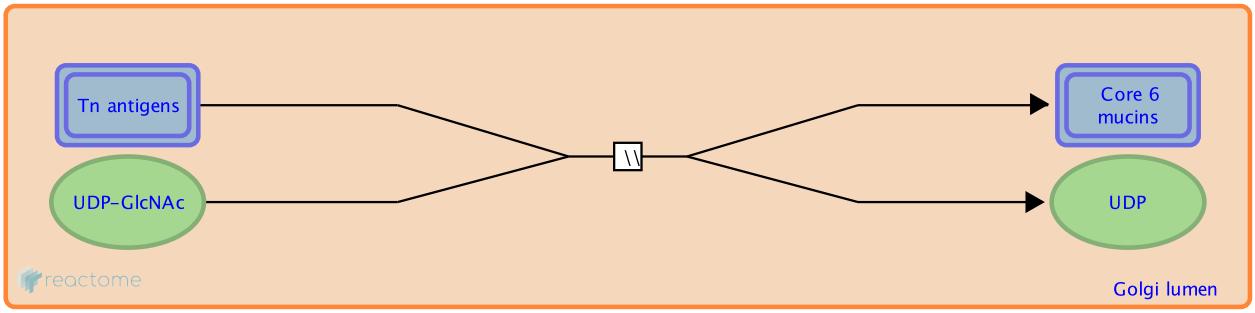
Addition of GlcNAc to the Tn antigen via a beta-1,6 linkage forms a Core 6 glycoprotein ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-914008

Type: omitted

Compartments: Golgi lumen



An unknown N-acetylglucosaminyltransferase mediates the transfer of GlcNAc to Tn antigens via an beta-1,6 linkage to create Core 6 mucins (Brockhausen et al. 2009).

Preceded by: GALNTs transfer GalNAc from UDP-GalNAc to mucins to form Tn antigens

Followed by: Addition of galactose to Core 6 glycoprotein

Literature references

Brockhausen, I., Schachter, H., Stanley, P. (2009). O-GalNAc Glycans, Essentials of Glycobiology, 2nd edition.

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

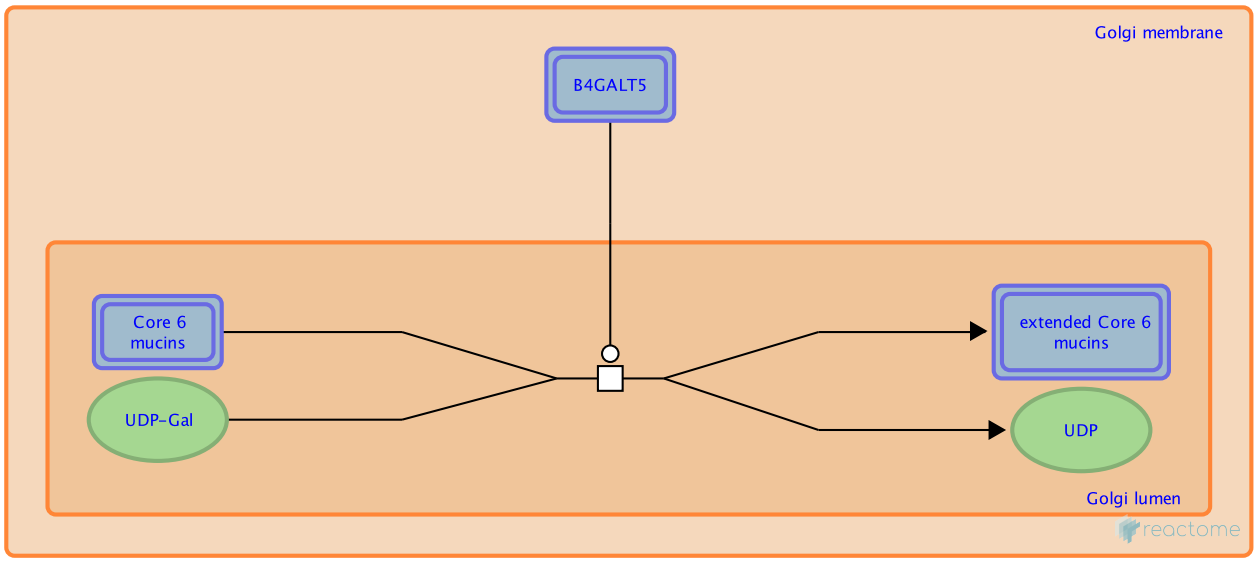
Addition of galactose to Core 6 glycoprotein ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-1964501

Type: transition

Compartments: Golgi lumen, Golgi membrane



Beta-1,4-galactosyltransferase 5 (B4GALT5) mediates the transfer of galactose from UDP-galactose to Core 6 glycoproteins (Sato et al. 1998).

Preceded by: Addition of GlcNAc to the Tn antigen via a beta-1,6 linkage forms a Core 6 glycoprotein

Literature references

Sato, T., Furukawa, K., Bakker, H., Van den Eijnden, DH., Van Die, I. (1998). Molecular cloning of a human cDNA encoding beta-1,4-galactosyltransferase with 37% identity to mammalian UDP-Gal:GlcNAc beta-1,4-galactosyltransferase. *Proc Natl Acad Sci U S A, 95*, 472-7. ↗

Editions

2011-11-04	Reviewed	Ferrer, A.

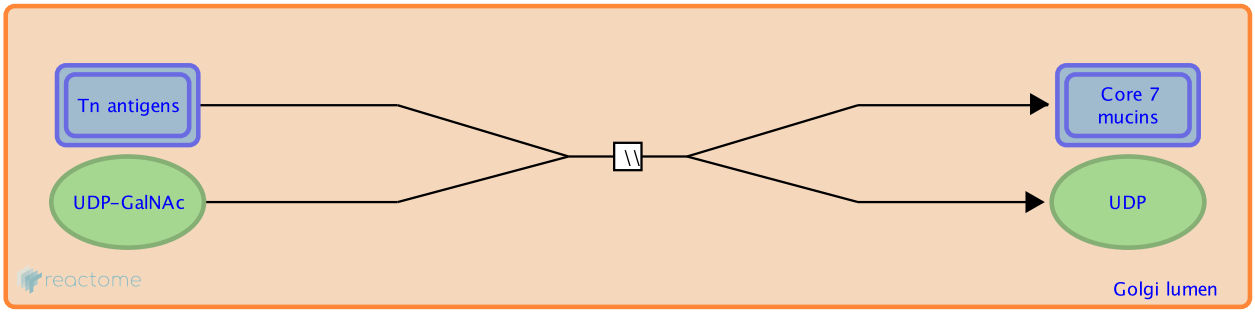
Addition of GalNAc to the Tn antigen via an alpha-1,6 linkage forms a Core 7 glycoprotein ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-914017

Type: omitted

Compartments: Golgi lumen



An unknown N-acetylgalactosaminyltransferase mediates the transfer of GalNAc is transferred to Tn antigens via an alpha-1,6 linkage to create Core 7 mucins (Brockhausen et al. 2009).

Preceded by: GALNTs transfer GalNAc from UDP-GalNAc to mucins to form Tn antigens

Literature references

Brockhausen, I., Schachter, H., Stanley, P. (2009). O-GalNAc Glycans, Essentials of Glycobiology, 2nd edition.

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

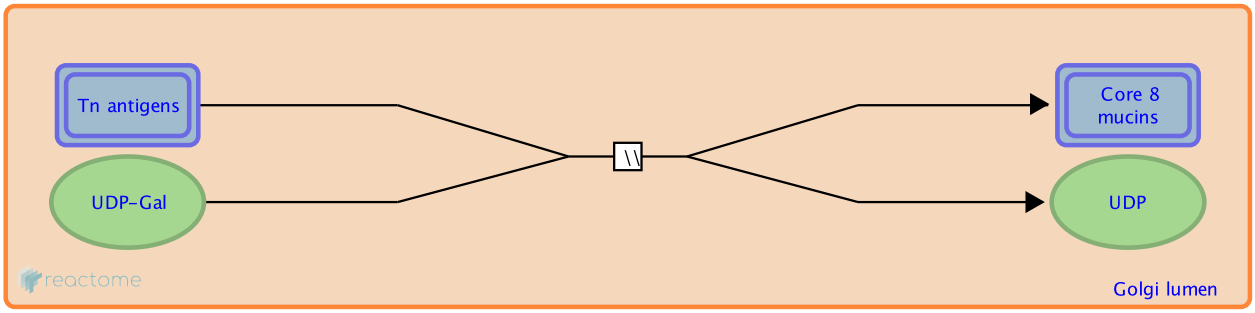
Addition of galactose to the Tn antigen via an alpha-1,3 linkage forms a Core 8 glycoprotein ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-914006

Type: omitted

Compartments: Golgi lumen



An unknown galactosyltransferase mediates the transfer of galactose is transferred to Tn antigens via an alpha-1,3 linkage to create Core 8 mucins (Brockhausen et al. 2009).

Preceded by: GALNTs transfer GalNAc from UDP-GalNAc to mucins to form Tn antigens

Literature references

Brockhausen, I., Schachter, H., Stanley, P. (2009). O-GalNAc Glycans, Essentials of Glycobiology, 2nd edition.

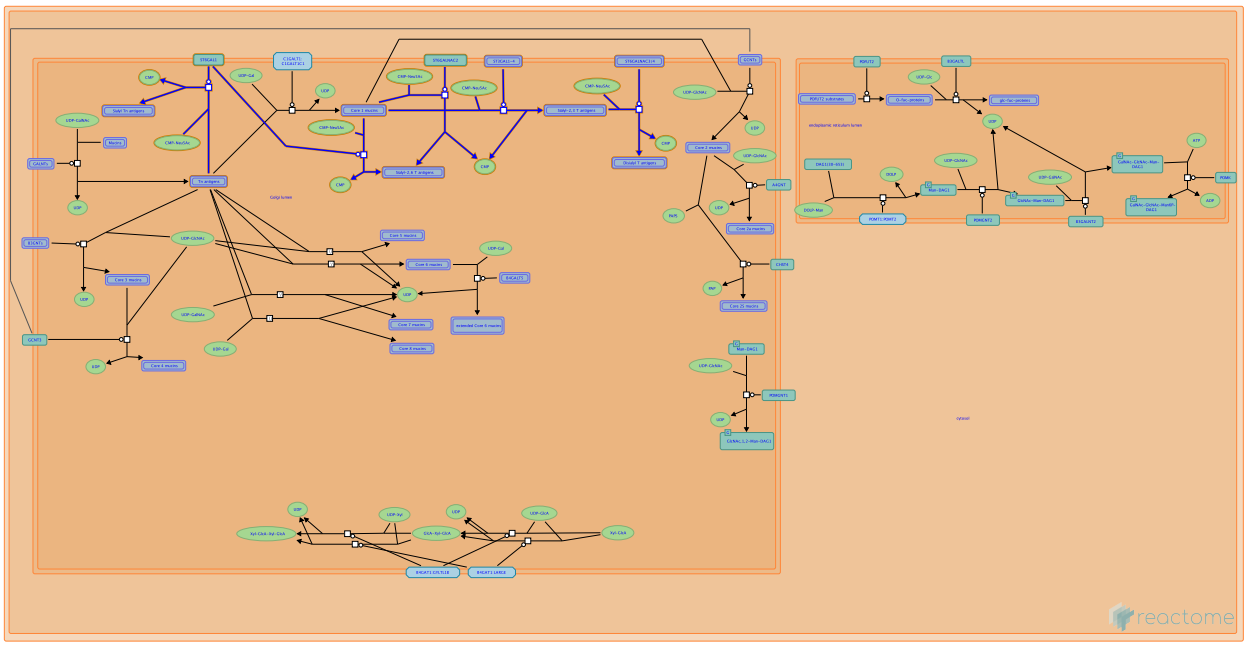
Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

Termination of O-glycan biosynthesis ↗

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-977068



O-glycan biosynthesis can be terminated (or modified) by the addition of sialic acid residues on Core 1 and 2 glycoproteins by sialyltransferases (Varki et al. 2009).

Literature references

Varki, A., Varki, A., Schauer, R., Cummings, RD., Esko, JD., Freeze, HH. et al. (2009). Sialic Acids.

Editions

2010-10-15	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

Table of Contents