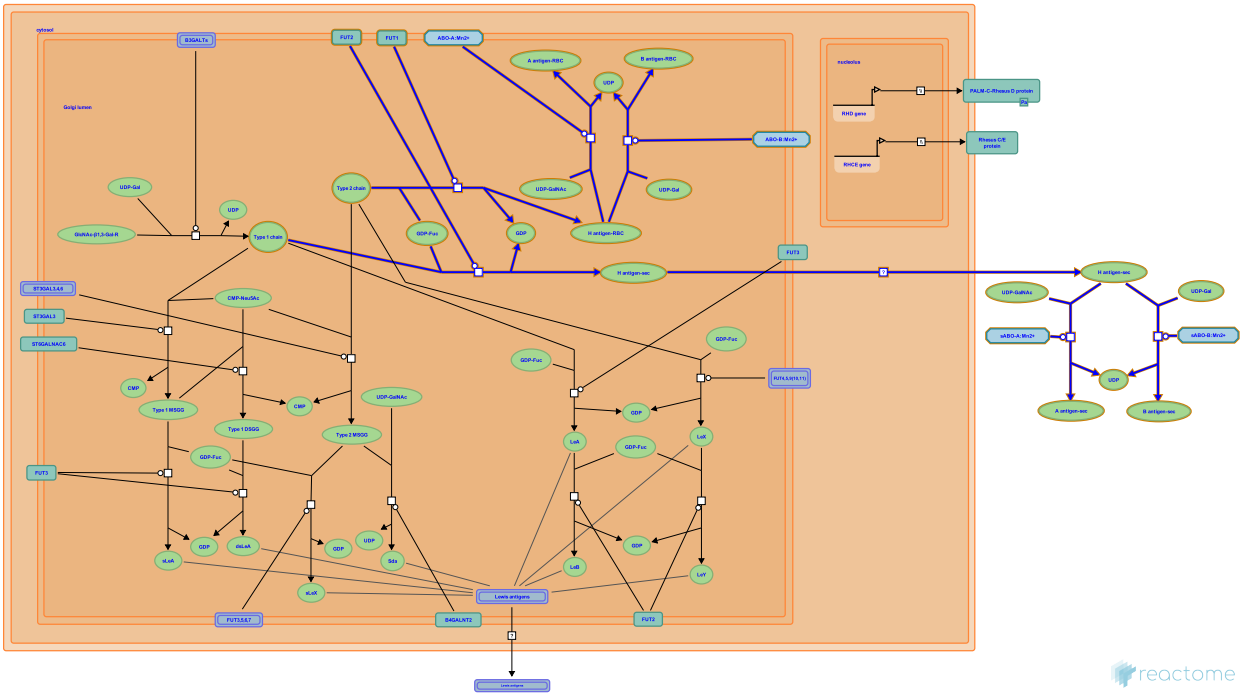
ABO blood group biosynthesis



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21/10/2020

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.

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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. ↗

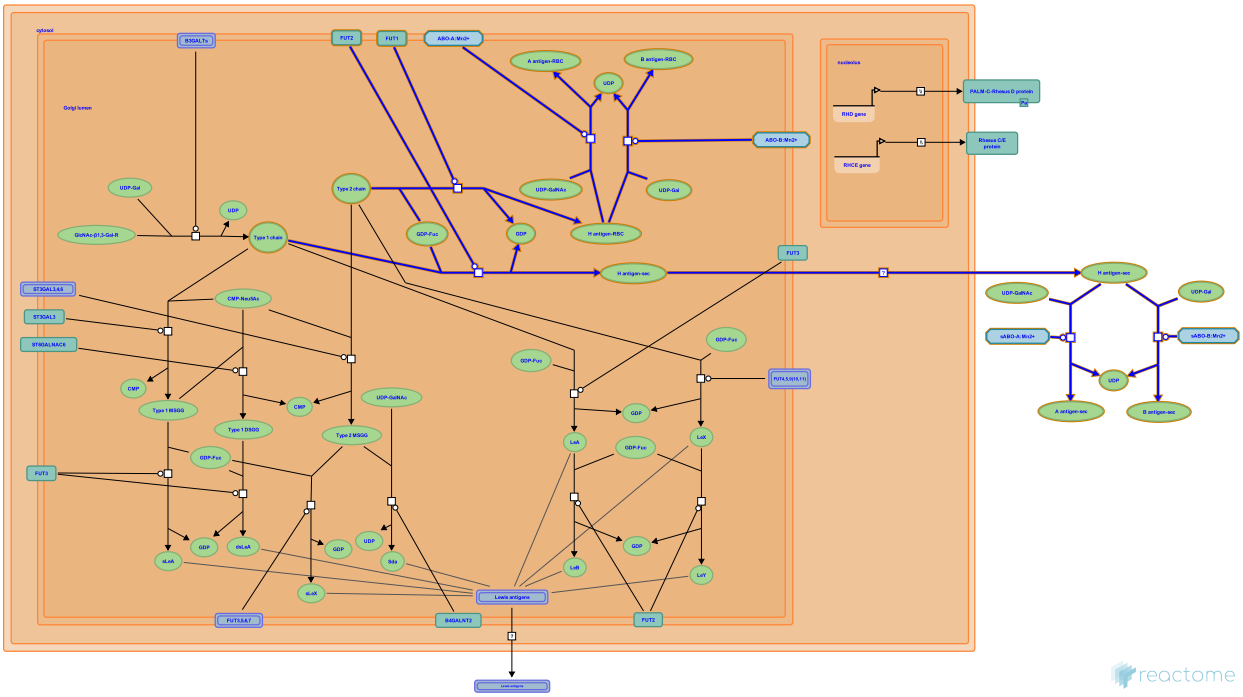
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

ABO blood group biosynthesis ↗

Stable identifier: R-HSA-9033807



Perhaps the most important and widely studied blood group is the ABO blood group. It consists of antigens found on the outer surface of red cells and corresponding antibodies in plasma. The majority of the world's population (~80%) are 'secretors' which means that the antigens present in their blood will also be found in other body fluids such as saliva. An individual can be a Secretor (Se) or a non-secretor (se) and this is completely independent of whether the individual is of blood type A, B, AB, or O. From a very early age, the immune system develops antibodies against whichever ABO blood group antigens are not found on the individual's RBCs. Thus, a blood group A individual will have anti-B antibodies and a blood group B individual will have anti-A antibodies. Individuals with the most common blood group, O, will have both anti-A and anti-B in their plasma. Blood group AB is the least common, and these individuals will have neither anti-A nor anti-B in their plasma.

The primary structure of these antigens is an oligosaccharide precursor sequence on to which one or more sugars are attached at specific locations. The blood group oligosaccharide antigens A, B and H are produced by enzymes expressed by these genes and form the basis of the ABO 'blood type' phenotypes. A and B antigens were originally identified on red blood cells (RBCs) but later identified on other cell types and in bodily secretions. The ABO blood group system is important in blood transfusion, cell/tissue/organ transplantation and forensic evidence at crime scenes.

The H antigen is formed with the addition of a fucose sugar onto one of two precursor oligosaccharide sequences (Type 1 chains are Gal β1,3 GlcNAc β1,3 Gal R and Type 2 chains are Gal β1,4 GlcNAc β1,3 Gal R; where R is a glycoprotein (Type 1) or glycosphingolipid (Type 2). Type 2 chains are only found on RBCs, epithelial cells and endothelial cells. The *H* gene expressed in hematopoietic cells produces α-1,2-fucosyltransferase 1 (FUT1) which adds a fucose to Type 2 chains to form the H antigen in non-secretors. Type 1 chains are found in secretors. The *Se* gene expressed in secretory glands produces α-1,2-fucosyltransferase 2 (FUT2) which adds a fucose to Type 1 chains to form the H antigen in secretors.

The H antigen is abundant in individuals with blood group O and is the essential precursor for the production of A and B antigens. A and B antigens are formed by the action of glycosyltransferases encoded by functional alleles at the ABO genetic locus. The co dominant A allele encodes A transferase, which

transfers an N acetylgalactosamine (GalNAc) sugar to the H antigen forming the A antigen. Similarly, the co dominant B allele encodes B transferase, which transfers a galactose (Gal) sugar to the H antigen forming the B antigen. Individuals who have both A and B alleles form the AB antigen. Individuals who are homozygous for the recessive O allele express the H antigen but do not form A or B antigens as they lack both the glycosyltransferase enzymes for their formation. Mutant alleles of the corresponding FUT1 or FUT2 genes result in either a H– phenotype (Bombay phenotype, Oh) or a weak H phenotype (para Bombay) where the affected individual cannot form H, A or B antigens (Kaneko et al. 1997, Koda et al. 1997). The biosyntheses of the A, B and H antigens are described in this section (Ewald & Sumner 2016, Scharberg et al. 2016).

Literature references

Kaneko, M., Nishihara, S., Shinya, N., Kudo, T., Iwasaki, H., Seno, T. et al. (1997). Wide variety of point mutations in the H gene of Bombay and para-Bombay individuals that inactivate H enzyme. *Blood, 90*, 839-49. ↗

Koda, Y., Soejima, M., Johnson, PH., Smart, E., Kimura, H. (1997). Missense mutation of FUT1 and deletion of FUT2 are responsible for Indian Bombay phenotype of ABO blood group system. *Biochem. Biophys. Res. Commun., 238*, 21-5. ↗

Scharberg, EA., Olsen, C., Bugert, P. (2016). The H blood group system. *Immunohematology, 32*, 112-118. ↗

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

Editions

2017-12-28	Authored, Edited	Jassal, B.
2018-12-17	Reviewed	Matsui, T.

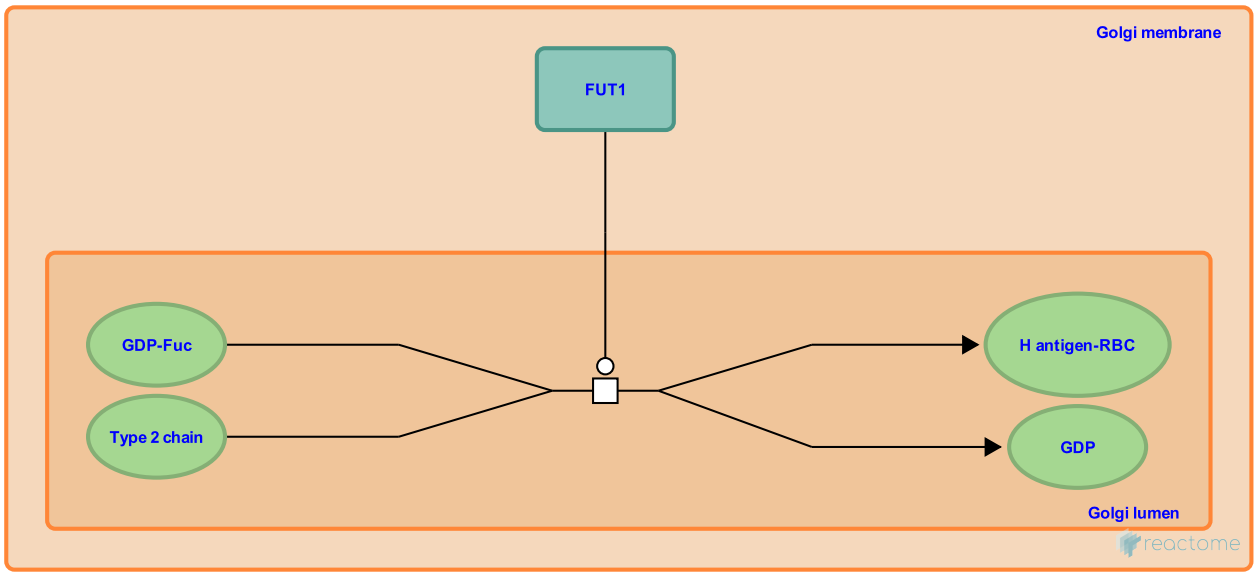
FUT1 transfers Fuc to Type 2 chains to form H antigen-RBC ↗

Location: ABO blood group biosynthesis

Stable identifier: R-HSA-9033949

Type: transition

Compartments: Golgi lumen, Golgi membrane



The H antigen is formed with the addition of a fucose (Fuc) sugar onto one of two precursor oligosaccharide sequences, Type 1 (RBCs) or Type 2 (secreted) chains. The *FUT1* gene (aka *H* gene) found in hematopoietic cells produces galactoside 2-α-L-fucosyltransferase 1 (FUT1 aka α-1,2-fucosyltransferase 1) which mediates the transfer of a fucose (Fuc) sugar to the galactose (Gal) sugar of the Type 2 chain precursor Gal-β1,4-GlcNAc-β1,3-Gal-R (where R is a glycosphingolipid) to form the H antigen (Larsen et al. 1990). This is an essential step for subsequent formation of A and B antigens. Mutations that inactivate the *FUT1* gene can result in the 'Bombay phenotype' where no A, B or H antigens are produced on RBCs (Koda et al 1997, Kaneko et al. 1997).

Followed by: ABO-A:Mn2+ transfers GalNAc to H antigen-RBC to form A antigen-RBC, ABO-B:Mn2+ transfers Gal to H antigen-RBC to form B antigen-RBC

Literature references

Larsen, RD., Ernst, LK., Nair, RP., Lowe, JB. (1990). Molecular cloning, sequence, and expression of a human GDP-L-fucose:beta-D-galactoside 2-alpha-L-fucosyltransferase cDNA that can form the H blood group antigen. *Proc. Natl. Acad. Sci. U.S.A., 87*, 6674-8. ↗

Kaneko, M., Nishihara, S., Shinya, N., Kudo, T., Iwasaki, H., Seno, T. et al. (1997). Wide variety of point mutations in the H gene of Bombay and para-Bombay individuals that inactivate H enzyme. *Blood, 90*, 839-49. ↗

Koda, Y., Soejima, M., Johnson, PH., Smart, E., Kimura, H. (1997). Missense mutation of FUT1 and deletion of FUT2 are responsible for Indian Bombay phenotype of ABO blood group system. *Biochem. Biophys. Res. Commun., 238*, 21-5. ↗

Editions

2017-12-29	Authored, Edited	Jassal, B.
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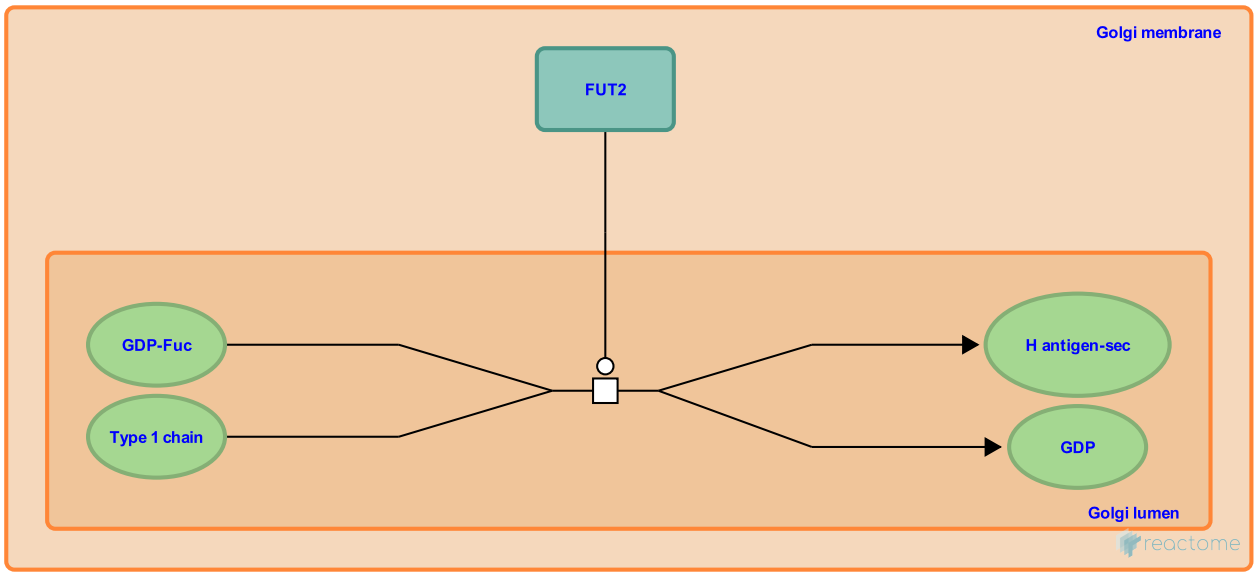
FUT2 transfers Fuc to Type 1 chains to form H antigen-sec ↗

Location: ABO blood group biosynthesis

Stable identifier: R-HSA-9036987

Type: transition

Compartments: Golgi lumen, Golgi membrane



The H antigen is formed by the addition of a fucose (Fuc) sugar onto one of two precursor oligosaccharide sequences; Type 1 or Type 2 chains. Type 2 chains are found on red blood cells (RBCs), epithelial cells and endothelial cells whereas Type 1 chains are primarily found in bodily secretions. The *FUT2* gene (aka *Se* gene) is expressed in secretory epithelial cells in salivary glands and the gastrointestinal tract and produces galactoside 2-α-L-fucosyltransferase 2 (FUT2 aka α-1,2-fucosyltransferase 2) which mediates the transfer of a Fuc sugar to the galactose (Gal) sugar of the Type 1 chain precursor Gal-β1,3-GlcNAc-β1,3-Gal-R (where R is a glycoprotein) to form the H antigen (Kelly et al. 1995, Koda et al. 1997). This is an essential step for subsequent formation of A and B antigens. Mutations that inactivate the *FUT2* gene can result in the 'Bombay phenotype' where no A, B or H antigens are produced in secretions (Koda et al 1997b, Kelly et al. 1994).

Followed by: H antigen-sec translocates from Golgi lumen to extracellular region

Literature references

Kelly, RJ., Rouquier, S., Giorgi, D., Lennon, GG., Lowe, JB. (1995). Sequence and expression of a candidate for the human Secretor blood group alpha(1,2)fucosyltransferase gene (FUT2). Homozygosity for an enzyme-inactivating nonsense mutation commonly correlates with the non-secretor phenotype. *J. Biol. Chem., 270*, 4640-9. ↗

Koda, Y., Soejima, M., Wang, B., Kimura, H. (1997). Structure and expression of the gene encoding secretor-type galactoside 2-alpha-L-fucosyltransferase (FUT2). *Eur. J. Biochem., 246*, 750-5. ↗

Kelly, RJ., Ernst, LK., Larsen, RD., Bryant, JG., Robinson, JS., Lowe, JB. (1994). Molecular basis for H blood group deficiency in Bombay (Oh) and para-Bombay individuals. *Proc. Natl. Acad. Sci. U.S.A., 91*, 5843-7. ↗

Koda, Y., Soejima, M., Johnson, PH., Smart, E., Kimura, H. (1997). Missense mutation of FUT1 and deletion of FUT2 are responsible for Indian Bombay phenotype of ABO blood group system. *Biochem. Biophys. Res. Commun., 238*, 21-5. ↗

Editions

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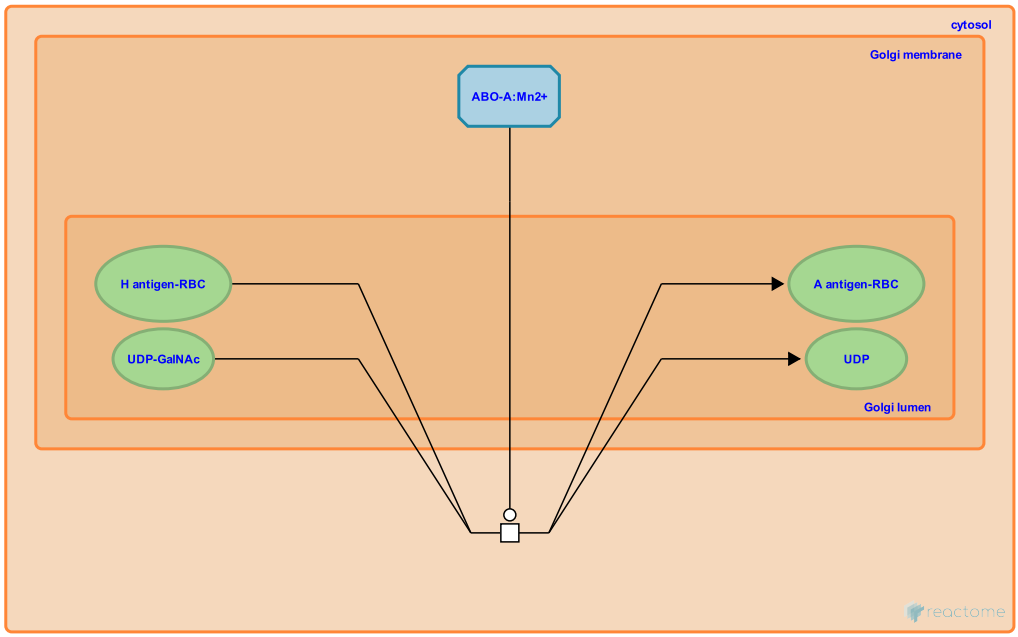
ABO-A:Mn2+ transfers GalNAc to H antigen-RBC to form A antigen-RBC ↗

Location: ABO blood group biosynthesis

Stable identifier: R-HSA-9033959

Type: transition

Compartments: cytosol, Golgi membrane



The histo-blood group ABO system transferase (ABO) is the basis of the ABO blood group system. A, B and AB individuals express a glycosyltransferase activity that converts the H antigen to the A antigen (by addition of GalNAc), to the B antigen (by addition of Gal) or to the AB antigen (by the addition of both GalNAc and Gal). O group individuals lack such activity. Differences in four critical amino acids (176, 235, 266 and 268) alter the specificity from an A to a B glycosyltransferase (Yamamoto et al. 1990, Yamamoto & McNeill 1996, Seto et al. 1999, Alfaro et al. 2008). The histo-blood group A transferase (ABO-A) utilises UDP-GalNAc to transfer N-acetylgalactosamine (GalNAc) to the H antigen formed via Type 2 chains to form the A antigen (Patenaude et al. 2002, Persson et al. 2007).

Preceded by: FUT1 transfers Fuc to Type 2 chains to form H antigen-RBC

Literature references

Persson, M., Letts, JA., Hosseini-Maaf, B., Borisova, SN., Palcic, MM., Evans, SV. et al. (2007). Structural effects of naturally occurring human blood group B galactosyltransferase mutations adjacent to the DXD motif. *J. Biol. Chem., 282*, 9564-70. ↗

Patenaude, SI., Seto, NO., Borisova, SN., Szpacenko, A., Marcus, SL., Palcic, MM. et al. (2002). The structural basis for specificity in human ABO(H) blood group biosynthesis. *Nat. Struct. Biol., 9*, 685-90. ↗

Yamamoto, F., Clausen, H., White, T., Marken, J., Hakomori, S. (1990). Molecular genetic basis of the histo-blood group ABO system. *Nature, 345*, 229-33. ↗

Seto, NO., Compston, CA., Evans, SV., Bundle, DR., Narang, SA., Palcic, MM. (1999). Donor substrate specificity of recombinant human blood group A, B and hybrid A/B glycosyltransferases expressed in Escherichia coli. *Eur. J. Biochem., 259*, 770-5. ↗

Yamamoto, F., McNeill, PD. (1996). Amino acid residue at codon 268 determines both activity and nucleotide-sugar donor substrate specificity of human histo-blood group A and B transferases. In vitro mutagenesis study. *J. Biol. Chem., 271*, 10515-20. ↗

Editions

2017-12-29	Authored, Edited	Jassal, B.
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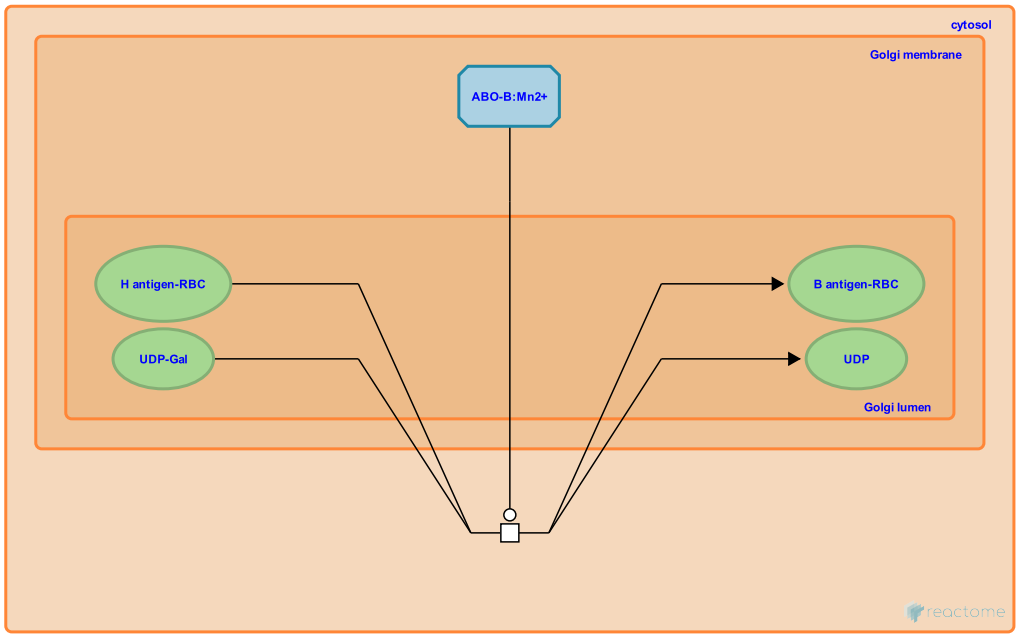
ABO-B:Mn2+ transfers Gal to H antigen-RBC to form B antigen-RBC ↗

Location: ABO blood group biosynthesis

Stable identifier: R-HSA-9033961

Type: transition

Compartments: cytosol, Golgi membrane



The histo-blood group ABO system transferase (ABO) is the basis of the ABO blood group system. A, B and AB individuals express glycosyltransferase activity that converts the H antigen to the A antigen (by addition of GalNAc), to the B antigen (by addition of Gal) or to the AB antigen (by the addition of both GalNAc and Gal). O group individuals lack such activity. Differences in four critical amino acids (176, 235, 266 and 268) alter the specificity from an A to a B glycosyltransferase (Yamamoto et al. 1990, Yamamoto & McNeill 1996, Seto et al. 1999, Alfaro et al. 2008). The histo-blood group B transferase (ABO-B) utilises UDP-Gal to transfer galactose (Gal) to the H antigen formed via Type 2 chains to form the B antigen (Patenaude et al. 2002, Persson et al. 2007).

Preceded by: FUT1 transfers Fuc to Type 2 chains to form H antigen-RBC

Literature references

Yamamoto, F., McNeill, PD. (1996). Amino acid residue at codon 268 determines both activity and nucleotide-sugar donor substrate specificity of human histo-blood group A and B transferases. In vitro mutagenesis study. *J. Biol. Chem., 271*, 10515-20. ↗

Seto, NO., Compston, CA., Evans, SV., Bundle, DR., Narang, SA., Palcic, MM. (1999). Donor substrate specificity of recombinant human blood group A, B and hybrid A/B glycosyltransferases expressed in Escherichia coli. *Eur. J. Biochem., 259*, 770-5. ↗

Yamamoto, F., Clausen, H., White, T., Marken, J., Hakomori, S. (1990). Molecular genetic basis of the histo-blood group ABO system. *Nature, 345*, 229-33. ↗

Persson, M., Letts, JA., Hosseini-Maaf, B., Borisova, SN., Palcic, MM., Evans, SV. et al. (2007). Structural effects of naturally occurring human blood group B galactosyltransferase mutations adjacent to the DXD motif. *J. Biol. Chem., 282*, 9564-70. ↗

Patenaude, SI., Seto, NO., Borisova, SN., Szpacenko, A., Marcus, SL., Palcic, MM. et al. (2002). The structural basis for specificity in human ABO(H) blood group biosynthesis. *Nat. Struct. Biol., 9*, 685-90. ↗

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2017-12-29	Authored, Edited	Jassal, B.
2018-12-17	Reviewed	Matsui, T.

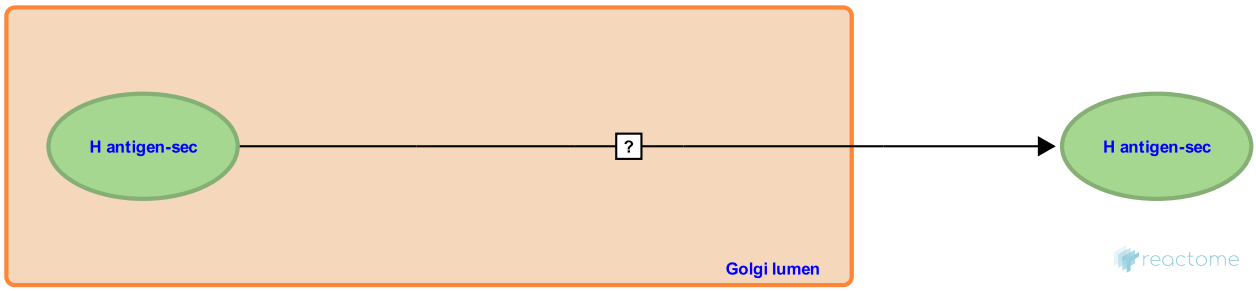
H antigen-sec translocates from Golgi lumen to extracellular region ↗

Location: ABO blood group biosynthesis

Stable identifier: R-HSA-9037612

Type: uncertain

Compartments: Golgi lumen, extracellular region



The H antigen in secretors (H antigen-sec) translocates from the Golgi lumen to the extracellular region by an unknown mechanism (Ewald & Sumner 2016). Here, it can be extended by the soluble forms of the histo-blood group ABO system transferase (sABO) enzymes.

Preceded by: FUT2 transfers Fuc to Type 1 chains to form H antigen-sec

Followed by: sABO-B:Mn2+ transfers Gal to H antigen-sec to form B antigen, sABO-A:Mn2+ transfers GalNAc to H antigen-sec to form A antigen-sec

Literature references

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

Editions

2018-02-20	Authored, Edited	Jassal, B.
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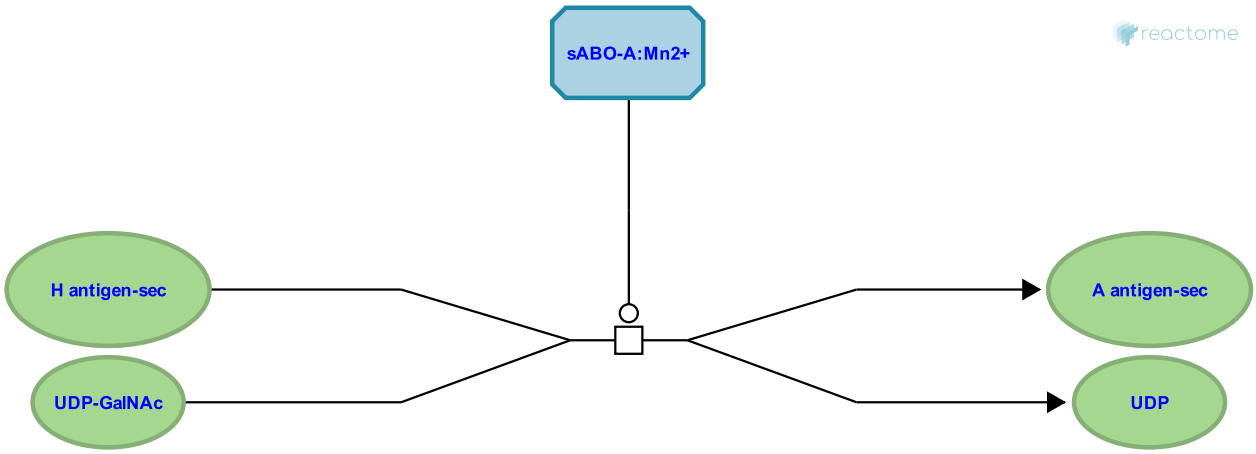
sABO-A:Mn2+ transfers GalNAc to H antigen-sec to form A antigen-sec ↗

Location: ABO blood group biosynthesis

Stable identifier: R-HSA-9034042

Type: transition

Compartments: extracellular region



As well as being a Golgi membrane resident, the histo-blood group ABO system transferase (ABO) can be proteolytically processed by an unknown protease into a soluble form, fucosylglycoprotein alpha-N-acetylgalactosaminyltransferase (sABO). A, B and AB individuals express glycosyltransferase activities that convert the H antigen to the A antigen (by addition of GalNAc), to the B antigen (by addition of Gal) or to the AB antigen (by the addition of both GalNAc and Gal). O group individuals lack such activity. Differences in four critical amino acids (176, 235, 266 and 268) alter the specificity from an A to a B glycosyltransferase (Yamamoto et al. 1990, Yamamoto & McNeill 1996, Seto et al. 1999, Alfaro et al. 2008). The soluble form of histo-blood group A transferase (sABO-A) utilises UDP-GalNAc to transfer N-acetylgalactosamine (GalNAc) to the H antigen formed via Type 1 chains to form the A antigen in secretors (A antigen-sec) (Patenaude et al. 2002, Persson et al. 2007).

Preceded by: H antigen-sec translocates from Golgi lumen to extracellular region

Literature references

Persson, M., Letts, JA., Hosseini-Maaf, B., Borisova, SN., Palcic, MM., Evans, SV. et al. (2007). Structural effects of naturally occurring human blood group B galactosyltransferase mutations adjacent to the DXD motif. *J. Biol. Chem., 282*, 9564-70. ↗

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Yamamoto, F., Clausen, H., White, T., Marken, J., Hakomori, S. (1990). Molecular genetic basis of the histo-blood group ABO system. *Nature, 345*, 229-33. ↗

Seto, NO., Compston, CA., Evans, SV., Bundle, DR., Narang, SA., Palcic, MM. (1999). Donor substrate specificity of recombinant human blood group A, B and hybrid A/B glycosyltransferases expressed in Escherichia coli. *Eur. J. Biochem., 259*, 770-5. ↗

Yamamoto, F., McNeill, PD. (1996). Amino acid residue at codon 268 determines both activity and nucleotide-sugar donor substrate specificity of human histo-blood group A and B transferases. In vitro mutagenesis study. *J. Biol. Chem., 271*, 10515-20. ↗

Editions

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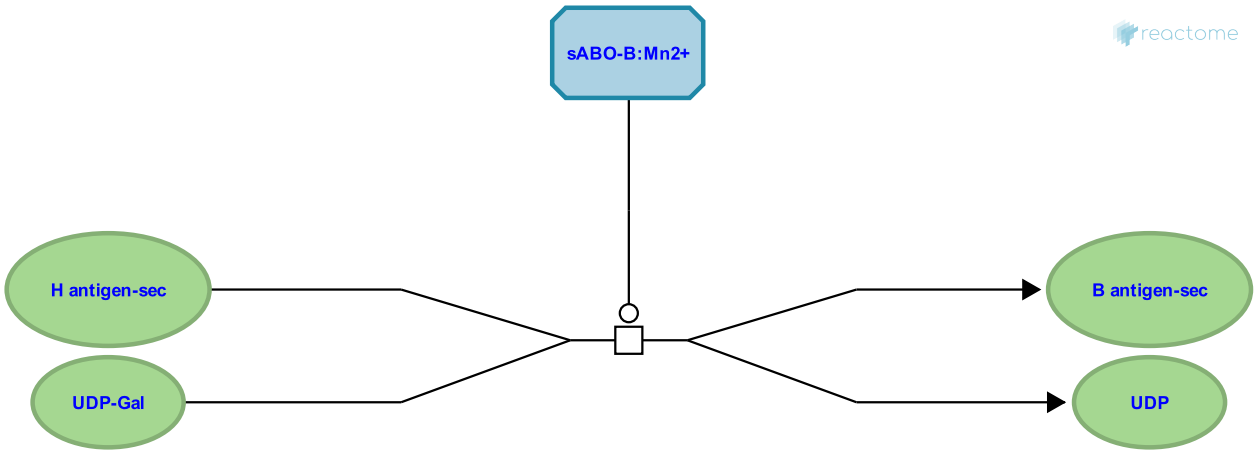
sABO-B:Mn2+ transfers Gal to H antigen-sec to form B antigen ↗

Location: ABO blood group biosynthesis

Stable identifier: R-HSA-9034053

Type: transition

Compartments: extracellular region



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Preceded by: H antigen-sec translocates from Golgi lumen to extracellular region

Literature references

Yamamoto, F., McNeill, PD. (1996). Amino acid residue at codon 268 determines both activity and nucleotide-sugar donor substrate specificity of human histo-blood group A and B transferases. In vitro mutagenesis study. *J. Biol. Chem., 271*, 10515-20. ↗

Seto, NO., Compston, CA., Evans, SV., Bundle, DR., Narang, SA., Palcic, MM. (1999). Donor substrate specificity of recombinant human blood group A, B and hybrid A/B glycosyltransferases expressed in Escherichia coli. *Eur. J. Biochem., 259*, 770-5. ↗

Yamamoto, F., Clausen, H., White, T., Marken, J., Hakomori, S. (1990). Molecular genetic basis of the histo-blood group ABO system. *Nature, 345*, 229-33. ↗

Persson, M., Letts, JA., Hosseini-Maaf, B., Borisova, SN., Palcic, MM., Evans, SV. et al. (2007). Structural effects of naturally occurring human blood group B galactosyltransferase mutations adjacent to the DXD motif. *J. Biol. Chem., 282*, 9564-70. ↗

Patenaude, SI., Seto, NO., Borisova, SN., Szpacenko, A., Marcus, SL., Palcic, MM. et al. (2002). The structural basis for specificity in human ABO(H) blood group biosynthesis. *Nat. Struct. Biol., 9*, 685-90. ↗

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2018-12-17	Reviewed	Matsui, T.

Table of Contents