O-linked glycosylation of mucins

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


**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**


Reactome database release: 82

This document contains 2 pathways and 12 reactions ([see Table of Contents](#))
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**


**Editions**

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https://reactome.org
**GALNTs transfer GalNAc to Mucins to form Tn antigens**

**Location:** O-linked glycosylation of mucins

**Stable identifier:** R-HSA-913675

**Type:** transition

**Compartments:** Golgi lumen, Golgi membrane

![Diagram of GALNTs transfer GalNAc to Mucins to form Tn antigens]

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. The Tn antigen is the simplest possible amino acid–carbohydrate glycoconjugate and comprises a GalNAc α-O-linked to either serine or threonine. In normal mammalian mucins, GalNAc is substituted by Gal, GlcNAc, or GalNAc forming up to eight different core structures. The unsubstituted Tn antigen is often found in cancer and is associated with poor prognosis (Kamerling 2007).

**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**


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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 lumen, Golgi membrane

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 to Mucins to form Tn antigens

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

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https://reactome.org
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 membrane, Golgi lumen

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

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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 lumen, Golgi membrane

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

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A4GNT transfers GlcNAc to core 2 mucins

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-5694487

Type: transition

Compartments: Golgi lumen, Golgi membrane

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


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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 lumen, Golgi membrane

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). This reaction occurs in the Golgi.

**Preceded by:** GALNTs transfer GalNAc to Mucins to form Tn antigens

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

**Literature references**


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https://reactome.org
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 lumen, Golgi membrane

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

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https://reactome.org
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 to Mucins to form Tn antigens

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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-acetylgalcosaminyltransferase 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 to Mucins to form Tn antigens

Followed by: Addition of galactose to Core 6 glycoprotein

Literature references


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Addition of galactose to Core 6 glycoprotein

Location: O-linked glycosylation of mucins

Stable identifier: R-HSA-1964501

Type: transition

Compartments: Golgi membrane, Golgi lumen

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


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 to Mucins to form Tn antigens

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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 to Mucins to form Tn antigens

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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


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