Glycobiology, 2017, vol. 27, no. 7, 601–618
doi: 10.1093/glycob/cwx034
Advance Access Publication Date: 4 May 2017
Review

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Review

Biological functions of fucose in mammals

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Received 18 February 2017; Revised 11 April 2017; Editorial decision 11 April 2017; Accepted 13 April 2017

Abstract

Fucose is a 6-deoxy hexose in the L-configuration found in a large variety of different organisms. In mammals, fucose is incorporated into *N*-glycans, *O*-glycans and glycolipids by 13 fucosyltransferases, all of which utilize the nucleotide-charged form, GDP-fucose, to modify targets. Three of the fucosyltransferases, FUT8, FUT12/POFUT1 and FUT13/POFUT2, are essential for proper development in mice. Fucose modifications have also been implicated in many other biological functions including immunity and cancer. Congenital mutations of a Golgi apparatus localized GDP-fucose transporter causes leukocyte adhesion deficiency type II, which results in severe developmental and immune deficiencies, highlighting the important role fucose plays in these processes. Additionally, changes in levels of fucosylated proteins have proven as useful tools for determining cancer diagnosis and prognosis. Chemically modified fucose analogs can be used to alter many of these fucose dependent processes or as tools to better understand them. In this review, we summarize the known roles of fucose in mammalian physiology and pathophysiology. Additionally, we discuss recent therapeutic advances for cancer and other diseases that are a direct result of our improved understanding of the role that fucose plays in these systems.

Key words: cancer, development, fucose, fucosyltransferase, immunology

Introduction

Fucose is an unusual sugar that is present in a variety of glycolipids and glycoproteins produced by mammalian cells. It is unique in having an L-configuration, whereas all other naturally occurring sugars in mammals exist in the D-conformation (Figure 1). It is also structurally distinct in lacking a hydroxyl group on the C-6 carbon (note contrast with D-galactose in Figure 1). A study of 3299 mammalian oligosaccharides revealed that fucose is found in 7.2% of oligosaccharides studied, second only to sialic acid, making fucose a relatively common component of glycan modifications on proteins and lipids (Werz et al. 2007).

Fucose can be incorporated into the terminal portions of *N*-, *O*- or lipid-linked oligosaccharide chains, modify the core of complex *N*-glycans, or can be linked directly to serine or threonine residues in some proteins. *N*-glycans are extremely structurally diverse, but all contain a 5-saccharide core with an *N*-acetylglucosamine (GlcNAc) attached to the amide nitrogen of asparagine within the appropriate consensus sequence (Asn-X-Ser/Thr) of target proteins (Stanley et al. 2009). Two types of *O*-glycans can be modified with fucose: mucin *O*-GalNAc glycans are initiated by the attachment of *N*-acetylgalactosamine (GalNAc) to the hydroxyl group of a serine or threonine; alternatively fucose can be directly attached to serine or threonine residues within the appropriate consensus sequence of a subset of proteins. There are 13 known fucosyltransferases responsible for the synthesis of this group of fucosylated glycans (Figure 2). The addition of fucose by these enzymes plays an important role in a variety of biological systems, many of which are discussed here. Knockout of three of these fucosyltransferases, FUT8, POFUT1 and POFUT2, is lethal to mice, demonstrating their biologic importance (Shi and Stanley 2003; Wang et al. 2005; Du et al. 2010).

All fucosyltransferases utilize a nucleotide-charged form of fucose, GDP-fucose, to modify target proteins or lipids. In mammals, GDP-fucose is synthesized through two pathways—the de novo synthesis pathway and the fucose salvage pathway (Figure 3).

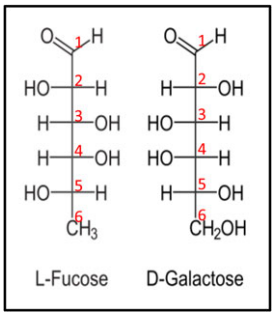

Fig. 1. Fischer projection formula of L-fucose. The six carbons of fucose are numbered. Note that most naturally occurring sugars, such as galactose, are present in the D-configuration, as can be determined by the arrangement of the hydroxyl group bound to the C-5 carbon. Note further that the C-6 carbon of L-fucose lacks a hydroxyl group present at the C-6 position of D-galactose. L-Fucose can also be described as 6-deoxy-L-galactose. This figure is available in black and white in print and in color at *Glycobiology* online.

The de novo pathway synthesizes GDP-fucose from GDP-mannose through a three-step reaction catalyzed by two enzymes, GDP-mannose 4,6-dehydratase and GDP-keto-6-deoxymannose 3,5 epimerase (the FX protein) (Ginsburg 1960; Tonetti et al. 1996). It is estimated that ~90% of GDP-fucose in mammals is generated by the de novo pathway under ordinary circumstances (Yurchenco and Atkinson 1975). The fucose salvage pathway utilizes free fucose derived from dietary sources or added to culture medium (Coffey et al. 1964; Kaufman and Ginsburg 1968). Fucose is transported across the plasma membrane through a poorly understood mechanism, perhaps L-fucose-specific facilitated diffusion (Wiese et al. 1994). A two-step mechanism catalyzed by two alternative enzymes then converts fucose to GDP-fucose (Ishihara et al. 1968). Once synthesized, GDP-fucose is transported into the lumen of the Golgi or endoplasmic reticulum (ER) to be used by fucosyltransferases. The Golgi transporter has been identified as SLC35C1, mutations in which result in the human disorder leukocyte adhesion deficiency type II (LAD2; see below) (Lühn et al. 2001). An ER-localized GDP-fucose transporter has been identified in *Drosophila* (Ishikawa et al. 2010), but the human ortholog of this gene has been shown to be a UDP-xylose/GlcNAc transporter (Ashikov et al. 2005). Identification of a candidate for a mammalian ER GDP-fucose transporter remains an open question. Fucose metabolism and function has been previously reviewed in detail (Becker and Lowe 2003). The remainder of this review will summarize the physiological and pathophysiological significance of fucose. Several very recent observations and their potential implications not covered in the earlier review will be emphasized.

Terminal fucosylation

Terminal fucosylation is a common modification found on many *N*-glycans, mucin *O*-GalNAc glycans and glycolipids. The processing and maturation of these glycans is quite complex and is carried out by the concerted action of a staggering number of enzymes. Ten fucosyltransferases (FUT1–7 and FUT9–11) are responsible for the addition of terminal fucose to these oligosaccharide chains. These fucosyltransferases are all localized to the Golgi apparatus and add fucose to oligosaccharides by α(1,2)-linkage to a terminal galactose or α(1,3/4)-linkage to a subterminal GlcNAc to generate blood group and Lewis antigens (Figure 2). Many of these enzymes serve redundant functions and thus, despite the biological importance of these modifications, loss of function for any one of these enzymes is not lethal in mice.

ABO blood groups

The ABO blood group antigens are perhaps the most well-known fucosylated glycans. Two α(1,2)fucosyltransferases, the H-transferase (FUT1) and the Secretor (Se) transferase (FUT2), synthesize the glycan known as the H-antigen by adding fucose to a terminal galactose residue (Lowe 1993). The H-transferase is expressed in erythroid precursors and is responsible for the generation of H-antigen on red blood cells (RBCs). The Se transferase is expressed in epithelial tissues and salivary glands and is responsible for the formation of H-antigen in saliva and other bodily secretions. Individuals without at least one copy of a functional FUT2 gene are considered nonsecretors and do not produce soluble H-antigen.

ABO locus-encoded glycosyltransferases can modify the H-antigen to generate A and B antigens in A, B or AB blood type individuals. In O blood type individuals, only unmodified H-antigen is expressed. These antigens are highly immunogenic and are found in high quantities on glycoproteins and glycolipids in RBCs. As a result, they notoriously prevent successful blood transfusion between incompatible individuals.

Patients lacking functional copies of both α(1,2)-FucT enzymes (FUT1 and FUT2), display the rare "Bombay phenotype" (present in only ~0.01% of the population) (Dipta and Hossain 2011), and are entirely deficient in type A, type B and H blood group antigens (Kelly et al. 1994). These individuals contain robust anti-A, anti-B and anti-H antibody titers and can only receive blood transfusions from other Bombay individuals (Davey et al. 1978). Similarly "para-Bombay" individuals lack functional copies of FUT1, but still have functional Se transferase (FUT2), resulting in the absence of blood group antigens only in RBCs (Wang et al. 1997). These individuals may have low titers of antibodies against the H-antigen, but can typically receive normal blood transfusions without complication (Lin-Chu and Broadberry 1990). Aside from potential issues with blood transfusions, these individuals appear unaffected, prompting questions about the physiological importance of these antigens.

Although the functional significance of ABO antigen expression remains unclear, ABO blood type has been linked with other processes, suggesting medical importance beyond blood typing. ABO blood type and ability to secrete soluble H-antigen have been linked with plasma von Willebrand Factor levels, a protein vital to the process of blood coagulation (Levy and Ginsburg 2001). Consequently, these characteristics are also related to von Willebrand disease and other related coagulopathies. ABO blood type has also been linked to increased risk for several types of cancer (Slater et al. 1993; Edgren et al. 2010; Wolpin et al. 2010), possibly suggesting a role in the immunogenicity of tumors and the associated opportunity for host recognition. The blood groups also appear to affect susceptibility to a number of pathogens (Ilver et al. 1998; Hutson et al. 2002; Huang et al. 2005; Wands et al. 2015) (discussed further below), suggesting that variation in blood types among individuals in a population might help to prevent the spread of disease.

Host–microbe interactions

Blood group antigens fucosylated by the Se transferase (FUT2) and Lewis fucosyltransferase (FUT3) also play an important role in mediating host–microbe interactions. *Helicobacter pylori*, a pathogen that can lead to peptic ulcer disease and gastric cancer, utilizes host expression of the Lewis^b antigen, generated by the joint action

Common Name(s)	Abbreviation	Representative Major Product(s)
H blood group α2fucosyltransferase	[a]FUT1	H antigen, type 2
Secretor (Se) blood group α2fucosyltransferase	[a]FUT2	H antigen, type 1
Fuc-TIII α3/4fucosyltransferase Lewis blood group fucosyltransferase	[a]FUT3	Sialyl-Lewis^x Sialyl-Lewis^a Lewis^b Lewis^x Lewis^a Lewis^y
Fuc-TIV α3fucosyltransferase ELAM-1 ligand fucosyl transferase	[a]FUT4	
Fuc-TV α3fucosyltransferase	[a]FUT5	
Fuc-TVI α3fucosyltransferase	[a]FUT6	
Fuc-TVII α3fucosyltransferase	[a]FUT7	
Fuc-TVIII α6fucosyltransferase	[b]FUT8	Core structure of all *N*-glycans "Core fucose"
Fuc-TIX α3fucosyltransferase	[a]FUT9	
Fuc-TX α3fucosyltransferase	[c]FUT10	Unknown
Fuc-TXI α3fucosyltransferase	[c]FUT11	Unknown
Protein *O*-fucosyltransferase 1	[d]POFUT1 / FUT12	Ser/Thr Ser/Thr
Protein *O*-fucosyltransferase 2	[e]POFUT2 / FUT13	Ser/Thr

Fig. 2. List of 13 known fucosyltransferases in humans. Major representative products of each fucosyltransferase are listed. The linkage of the fucose added by each enzyme appears in bold. [a]These enzymes can add fucose to oligosaccharide chains on glycolipids, *N*-glycans or mucin *O*-glycans. [b]This enzyme only adds the core fucose to *N*-glycans. [c]These are putative α3-fucosyltransferases. Acceptor substrates have not been clearly defined. [d]This modification is only observed in *O*-fucose consensus sequences on EGF repeats ($C^2XXXX(S/T)C^3$), see Figure 4A. [e]This modification is only observed in *O*-fucose consensus sequences on TSRs ($C^{1-2}XX(S/T)C^{2-3}$), see Figure 4B. This figure is available in black and white in print and in color at *Glycobiology* online.

of the Se and Lewis fucosyltransferases, to recognize and attach to gastric epithelial tissue (Ilver et al. 1998). Other pathogens including *Norovirus* (Xu et al. 2003; Huang et al. 2005) and *Vibrio cholera* (Wands et al. 2015) also take advantage of specific blood group antigens to attach to host cells. Additionally, *Bacteroides thetaiotaomicron*, a prominent resident of the human intestinal tract, can sense low fucose availability in the gut and induce expression of host fucosyltransferases. It is able to harvest fucose from secreted oligosaccharides using α-fucosidases (Xu et al. 2003). Other bacteria exploit the release of free fucose by *B. thetaiotaomicron* using their own fucose sensors (Pacheco et al. 2012).

Fucosyltransferases also play an important role in maintaining the gut microbiome. The activity of Se fucosyltransferase (FUT2) promotes normal microbial diversity and composition in the gut (Kashyap et al. 2013). Its up-regulation during illness serves as a protective mechanism to increase tolerance to infection and maintain host-microbiome symbiosis (Pham et al. 2014; Pickard et al. 2014). Inactivating FUT2 mutations, seen in about 20% of the human population (Hoskins 1967; Ikehara et al. 2001), result in a non-secretor phenotype that is associated with a distinct community of bacteria in the gut. Among the notable distinctions in nonsecretors is an increased association with the genus *Prevotella*, which can

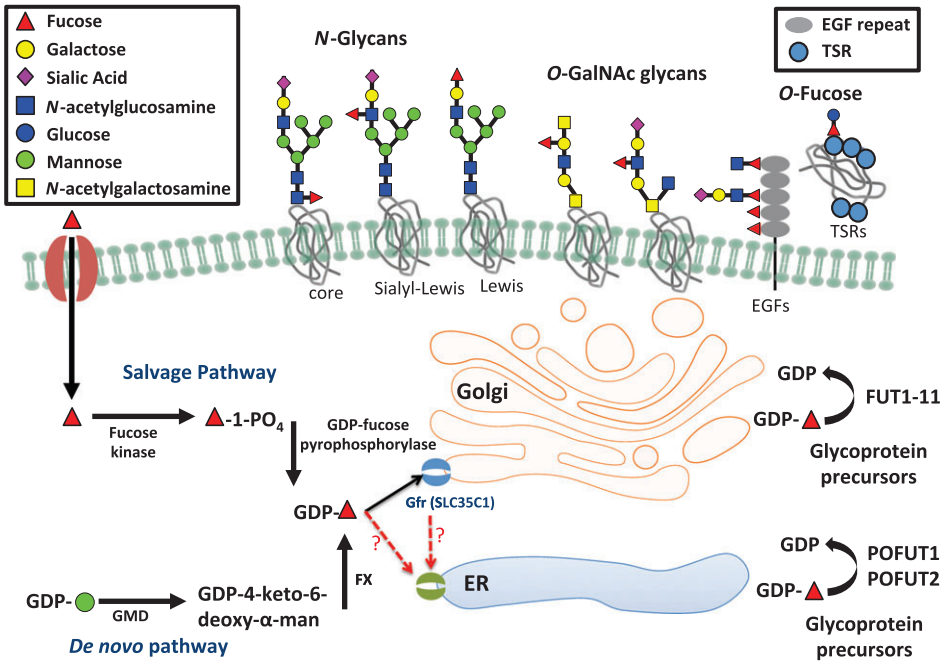

Fig. 3. Fucose metabolism pathways and variation in types of fucosylated glycans. This figure illustrates the de novo fucose synthesis pathway, which converts GDP-mannose to GDP-fucose and the fucose salvage pathway, which converts free fucose taken up from outside the cell to GDP-fucose. GDP-fucose can then be taken up into the Golgi apparatus by the GDP-fucose transporter (SLC35C1) and possibly into the ER by an as yet unknown transporter. Proteins are then modified with GDP-fucose and other carbohydrates within the Golgi and ER and can then be secreted or expressed on the cell surface. This figure is available in black and white in print and in color at *Glycobiology* online.

promote breakdown of the gut's mucus barrier (Rho et al. 2005; Rausch et al. 2011). Conversely, bacteria thought to promote good intestinal health including members of the *Lactobacillus* and *Bifidobacterium* genera are decreased in nonsecretors (Rausch et al. 2011; Wacklin et al. 2011). Abnormal gut microbiome composition with a disproportionately increased segment of bacteria associated with the nonsecretor phenotype can result in dysregulation of the local immune response (Xavier and Podolsky 2007) and is associated with increased risk of Crohn's disease, a chronic inflammatory bowel disease (Serpa et al. 2004; van Heel et al. 2004; McGovern et al. 2010).

Learning, memory and cognitive processes

Synaptic plasticity, neurite outgrowth and neuron morphology are regulated by fucosylation and are responsible for many cognitive processes including learning and memory. It was initially recognized that fucosylation of structures in the hippocampus was a component of learning and long-term potentiation (LTP) (Pohle et al. 1987). Further, injections of L-fucose enhance LTP in the rat brain (Krug et al. 1994). Additional work demonstrated that fucose α(1,2)-linkages formed by FUT1 and FUT2 were directly involved in synapse formation and neurite outgrowth (Kalovidouris et al. 2005). These fucose modifications can also direct neurite migration and mediate pathfinding for sensory neurons, including those in the olfactory bulb (Lipscomb et al. 2003; St John et al. 2006).

One glycoprotein involved in these processes that has been well characterized is Synapsin I, a protein involved in neurotransmitter release and the formation of new synapses. Fucosylation regulates turnover and stability of this protein (Murrey et al. 2006). Fucosylation of neural cell adhesion molecule has also been suggested to regulate its function (Pestean et al. 1995; Liedtke et al. 2001). More recent work suggests that a wide array of olfactory bulb proteins involved in cell adhesion, ion and solute transport, ATP binding, synaptic vesicle formation, and cell signaling are all modified with α (1,2)-fucose (Murrey et al. 2009). Fucosylation of these proteins contributes to olfactory bulb development (Murrey et al. 2009).

Leukocyte rolling and extravasation

Leukocyte trafficking is a process mediated by selectins and their counter-receptors (reviewed previously in Lowe (1997)). E-, P- and L-selectins are expressed in platelets (P-selectin), leukocytes (L-selectin) and endothelial cells (E- and P-selectins) allowing for their adhesion to oligosaccharide-containing ligands expressed by specialized endothelial cells lining postcapillary venules. Mucin *O*-GalNAc glycans can make up ~70% of these ligands by mass and are heavily decorated with fucose (Imai et al. 1991; Lowe 1997). Two α (1,3) fucosyltransferases, encoded by the FUT4 and FUT7 genes, are responsible for the addition of these fucose residues (Homeister et al. 2001). Inactivation of FUT7, in particular, causes a severe deficit in selectin-dependent endothelial cell adhesion and lymphocyte homing (Malý et al. 1996). Fucose modifications on glycolipid E-selectin receptors are required for neutrophil extravasation during inflammation (Malý et al. 1996; Nimrichter et al. 2008).

LAD2, a rare congenital disorder of glycosylation caused by mutation of the gene encoding a GDP-fucose transporter in the Golgi apparatus (SLC35C1), exemplifies the importance of fucose in leukocyte trafficking. LAD2 is characterized by immunodeficiency, leukocytosis without pus formation, mental retardation and growth retardation, all directly attributed to the absence of neutrophil sialyl Lewis^X, of which fucose is an essential component (Yakubenia et al. 2008). Dietary supplementation with fucose can reduce symptoms of LAD2 in some patients (Marquardt et al. 1999; Etzioni et al. 2002),

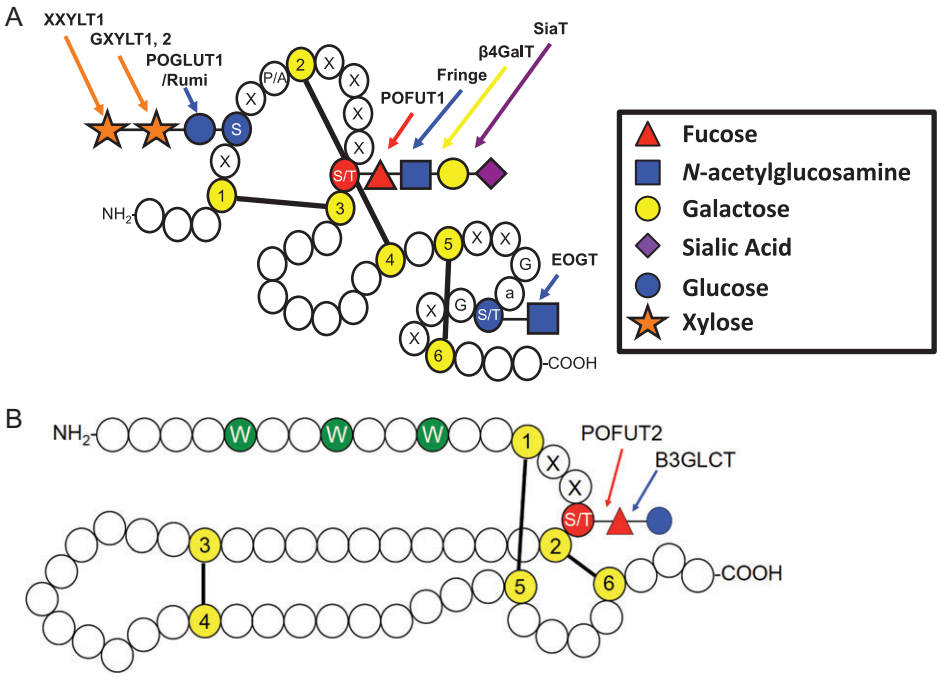

Fig. 4. Key features of EGF repeats and TSRs. (**A**) Cartoon showing a single EGF repeat. Each circle represents one amino acid. Conserved cysteines (yellow) are numbered and disulfide bonds are indicated. *O*-Glucose and *O*-GlcNAc sites are shaded blue and the *O*-fucose site is shaded red. Enzymes responsible for the addition of each sugar are indicated. Modified from Rana and Haltiwanger (2011). Used with permission. Elsevier. (**B**) Cartoon showing a typical TSR. Conserved cysteines (yellow) and disulfide bonds are indicated. *C*-Mannose sites are shown in green and the *O*-fucose site is shaded red. (S) Serine; (T) Threonine; (G) Glycine; (W) Tryptophan; (X) any amino acid, (a) any aromatic amino acid. Modified with permission from Haltiwanger (2004). ©Elsevier. This figure is available in black and white in print and in color at *Glycobiology* online.

including some with mutations causing complete inactivation of SLC35C1 (Hidalgo et al. 2003), suggesting that at high concentrations GDP-fucose might be transported to the Golgi by the more recently described SLC35C2 (Lu et al. 2010) or other as yet unknown transporters (Figure 3).

Cancer metastasis

As a byproduct of their role in promoting selectin-mediated rolling and adhesion, Sialyl Lewis antigens play an important role in promoting cancer migration and metastasis (Kannagi 1997). These antigens are upregulated in a variety of cancer types including lung (Zenita et al. 1988), breast (Jeschke et al. 2005) and colorectal (Kudo et al. 1998; Zipin et al. 2004) cancers and serve as prognostic factors for increased risk of metastasis (Itai et al. 1991). Studies have shown that elimination of terminal fucose from these antigens with an α-L-fucosidase can impair their ability to roll within endothelial tissue and decrease cancer cell invasion (Yuan et al. 2008). Additionally, one study demonstrated that preventing terminal fucosylation by knocking down FUT1 and FUT4 inhibits tumor growth (Zhang et al. 2008). Similarly, endogenous fucosidases have been shown to play a role in preventing cancer cell proliferation. Decreased expression of α-L-fucosidase 1 (FUCA1) has been identified in a number of different cancer types including colorectal (Otero-Estévez et al. 2013; Ezawa et al. 2016), gastric (Liu et al. 2009) and breast (Cheng et al. 2015) cancers.

Altered fucosylation has also been implicated in affecting TNF-related apoptosis inducing ligand activity in colon cancer, a ligand important for promoting destruction of transformed cells. Although the precise role for fucose in the regulation of this signaling pathway remains unclear (Haltiwanger 2009), defects in the de novo synthesis of GDP-fucose cause increased tumor growth and metastasis of colon cancer in mice (Moriwaki et al. 2009).

Fertilization and development

Fucosylated *N*-glycans in the zona pellucida facilitate sperm binding in a variety of mammalian species (Lefebvre et al. 1997; Yonezawa et al. 1997; Johnston et al. 1998), including humans (Pang et al. 2011). Fucosylated Lewis^X antigens also promote cell–cell adhesion in early stage embryos (Bird and Kimber 1984). Fuc-TIX encoded by the *FUT9* gene and responsible for the generation of Lewis^X in the brain plays an important role in neural development and promotes normal migration of motor neuron progenitors (Ohata et al. 2009). *Fut9* knockout in mice results in development of anxiety-like behavior (Kudo et al. 2007). Additionally, knockout of *Fut2* in mice resulted in altered hepatic vasculature and hepatic fibrosis resulting in microcirculatory disturbances and sensitivity toward bile salt toxicity (Maroni et al. 2017).

Core fucosylation

Fucosylation on the GlcNAc linked to asparagine in the core of *N*-glycans (core fucosylation) is the most common type of fucose modification. It occurs exclusively on *N*-glycans. Like terminal fucosylation, core fucosylation occurs in the Golgi and is characterized by α(1,6)-linkage to the innermost GlcNAc of the *N*-glycan core (Figure 2). However, while enzymes responsible for terminal fucosylation may catalyze the formation of redundant linkages, FUT8 is the sole enzyme responsible for catalyzing this reaction. *Fut8* knockout mice lack core fucose, and while born with no apparent

anomalies, about 70% die within three days of birth due to major developmental growth and respiratory defects (Wang et al. 2005, 2006b). Survivors display severe growth retardation and emphysema-like changes in the lungs. Core fucosylation of α3β1 integrin also plays a critical role in kidney and lung organogenesis (Kreidberg et al. 1996).

Inflammation and the immune system

Core fucosylation of *N*-glycans plays several important roles in regulating the immune system. Perhaps of greatest interest is the observation that antibody dependent cellular cytotoxicity (ADCC) is inhibited by the presence of fucose on the Fc region of IgG1 antibodies. Core fucose on IgG1 *N*-glycans causes a 50- to 100-fold reduction in binding to FcγRIIIa (CD16), an Fc receptor found on the surface of natural killer cells and macrophages that is partially responsible for crosslinking these immune effector cells with antibody-bound cells targeted for destruction (Shields et al. 2002). A co-crystal structure demonstrated that the addition of this core fucose causes a steric clash that weakens carbohydrate–carbohydrate interactions required for high affinity receptor recognition (Ferrara et al. 2011). This observation is of particular importance because therapeutic antibodies, used in the treatment of cancer and other diseases, can be generated without this core fucose to significantly enhance their potency (Shields et al. 2002; Shinkawa et al. 2003).

Several pharmaceutical companies have begun to take advantage of this knowledge and glycoengineered monoclonal antibodies (mAb) are being developed for therapeutic purposes (Yamane-Ohnuki and Satoh 2009). Two afucosylated mAbs have already been approved by the FDA for use in cancer patients: mogamulizumab and obinutuzumab. Mogamulizumab targets chemokine receptor 4, an important signal transducer that is upregulated in T-cell leukemia and lymphoma (Ishii et al. 2010; Beck and Reichert 2012). Obinutuzumab is an afucosylated mAb against CD20, an antigen found on developing B-cells, and has been effective for the treatment of chronic lymphocytic leukemia (CLL). Rituximab, a mAb also targeting CD20, has been approved for use in autoimmune diseases and CLL since 1997. However, obinutuzumab has been shown to be more effective in CLL treatment due to more efficient promotion of ADCC (Illidge et al. 2015). Inspired by these successes, drug companies have continued development of similarly glycoengineered mAbs and have more than 20 currently in clinical trials (Hamadani et al. 2013; Wei et al. 2013; Sathish 2014; Gardai et al. 2015).

While enhanced activation of ADCC by afucosylated antibodies has proven useful in the development of cancer therapeutics, in the setting of dengue virus infection the same phenomenon contributes to antibody dependent enhancement of disease. Only about 15% of individuals infected by dengue virus progress to more severe hemolytic disease (dengue hemorrhagic fever or dengue shock syndrome) (Vaughn et al. 2000). A recent report has demonstrated that patients with a high percentage of afucosylated antibodies targeting a dengue envelope protein are more likely to develop acute hemolytic disease (Wang et al. 2017).

Additionally, inflammatory cytokines TGFβ1 and α3β1 require core fucose to function (Kreidberg et al. 1996; Wang et al. 2005). Down-regulation of these signaling pathways causes enhanced matrix metalloproteinase expression and inflammation. Lack of core fucosylation also disrupts epidermal growth factor receptor (Wang et al. 2006a) and vascular endothelial growth factors mediated signaling (Wang et al. 2009). Core fucosylation is vital for appropriate growth factor receptor signaling (Wang et al. 2005, 2006b).

Cancer and cancer biomarkers

Many fucosylated glycans on glycoproteins serve as important cancer biomarkers (Miyoshi et al. 2008; Adamczyk et al. 2012). Elevated α-fetoprotein (AFP) levels are a well-established marker for hepatocellular carcinoma. Unfortunately, elevated AFP is not entirely specific for cancer, and may also be associated with other forms of benign liver disease (i.e., cirrhosis or hepatitis). Only in hepatocellular carcinoma, however, is the fraction of core fucosylated AFP elevated, making this a more reliable biomarker for cancer (Aoyagi et al. 1998; Flores and Marrero 2014). In prostate cancer, prostate-specific antigen (PSA) is another well-established "tumor-specific" biomarker that lacks true specificity as it may also be elevated in benign prostatic hyperplasia (BPH), a very common diagnostic confounder. In patients with prostate cancer, the fraction of core fucosylated PSA is significantly increased relative to patients with BPH (Saldova et al. 2011), again increasing the value of this biomarker. Increases in core fucosylation of serum proteins have also been associated with increased risk of metastasis in prostate cancer (Kyselova et al. 2007). In pancreatic cancer, core fucosylated haptoglobin is another potential biomarker for cancer detection (Okuyama et al. 2006; Miyoshi and Nakano 2008). Pancreatic cancer has a very poor prognosis largely due to a lack of reliable early detection methods, so the discovery and development of more reliable detection biomarkers would be of tremendous clinical utility (Goggins 2005).

Additionally, increased core fucosylation of *N*-glycans on E-cadherin and integrins has been shown to decrease cell adhesion and promote cell migration and metastasis in cancer (Zhao et al. 2006, 2008). Increased expression of FUT8 promotes this mechanism causing increased tumor growth and metastasis in nonsmall cell lung cancer and ovarian cancer (Yan et al. 2010; Chen et al. 2013). FUT8 inhibitors might rationally be developed as antineoplastic agents in this context.

O-Fucosylation

Fucose is also added directly to serine or threonine residues on proteins by two protein *O*-fucosyltransferases: POFUT1 (FUT12) or POFUT2 (FUT13). Both POFUT1 and POFUT2 are essential for development in mice and are widely expressed in embryonic and adult tissues (Shi and Stanley 2003; Du et al. 2010). POFUT1 is responsible for the addition of fucose to epidermal growth factor-like (EGF) repeats containing the consensus sequence $C^2XXXX(S/T)C^3$, where C^2 and C^3 are the second and third conserved cysteines of the EGF repeat and X represents any amino acid (Shao et al. 2003; Müller et al. 2014) (Figure 4A). EGF repeats can also be modified with *O*-glucose and *O*-GlcNAc at distinct consensus sequences. POFUT2 is responsible for transferring fucose to serine or threonine on thrombospondin type 1 repeats (TSRs) with the consensus sequence $C^1XX(S/T)C^2$ in group 1 TSRs and $C^2XX(S/T)C^3$ in group 2 TSRs (Luo et al. 2006a; 2006b; Valero-González et al. 2016) (Figure 4B). TSRs can also be modified with C-mannosylation of tryptophans (de Peredo et al. 2002). Both EGF repeats and TSRs contain six conserved cysteines, which form three disulfide bonds that are crucial for the structure of these motifs. POFUT1 and POFUT2 only modify properly folded EGF repeats and TSRs, respectively (Wang and Spellman 1998; Luo et al. 2006). Over 100 proteins contain EGF repeats with consensus sequences for *O*-fucose modification by POFUT1 (Rampal et al. 2007) (Table I) and about 50 proteins contain TSRs with *O*-fucose consensus sequences for modification by

POFUT2 (Leonhard-Melief and Haltiwanger 2010) (Table II). Modification of many of these proteins remains unconfirmed and much remains to be determined about roles of *O*-fucose on these proteins. Unlike the other fucosyltransferases in Figure 2, the protein *O*-fucosyltransferases are localized in the ER (Luo and Haltiwanger 2005; Okajima et al. 2005; Luo et al. 2006). The fact that POFUT1 and POFUT2 only modify properly folded modules and are ER-localized has led to the hypothesis that both enzymes participate in quality control (Vasudevan and Haltiwanger 2014).

O-Fucosylation of EGF repeats

The Notch family of receptors has more predicted *O*-fucose sites than any other protein (see Table I) (Moloney et al. 2000b). *Pofut1* knockout is embryonic lethal in mice (Shi and Stanley 2003; Okamura and Saga 2008). These knockout mice show severe growth retardation during early embryogenesis, particularly in somite formation. Neural tube, cardiac and blood vessel defects are also evident in these mice—all phenotypes associated with defects in Notch signaling. POFUT1 also plays a critical role in mediating other Notch dependent processes including promotion of T-cell differentiation during lymphopoiesis (Yao et al. 2011). Results from many groups reveal that POFUT1 is essential for normal Notch-ligand binding and Notch signaling (Shi and Stanley 2003; Okajima et al. 2005; Rampal et al. 2005; Stahl et al. 2008; Kakuda and Haltiwanger 2017). Recently reported Notch1-DLL4 (Luca et al. 2015) and Notch1-JAG1 (Luca et al. 2017) cocrystal structures have additionally shown that the fucose on EGF repeat 12 of the extracellular domain of Notch1 directly interacts with the Notch activating ligand DLL4, and the fucose on EGF repeats 8 and 12 interact with JAG1, demonstrating the potential importance of these fucose residues at the interface of protein-protein interactions. In addition to its fucosyltransferase activity, the *Drosophila* homolog of POFUT1, Ofut1, also acts as a chaperone for Notch protein folding (Okajima et al. 2005), although it is not clear that this function is conserved in mammalian systems (Stahl et al. 2008).

Fringe enzymes can elongate *O*-fucose residues with a GlcNAc to further regulate Notch signaling (Figure 4A) (Moloney et al. 2000a). Fringe was originally described in *Drosophila*, where it was recognized that mutations in *fringe* caused a Notching phenotype in wings (Irvine and Wieschaus 1994). Further work demonstrated that Fringe is an important regulator of Notch signaling (Panin et al. 1997; Klein and Arias 1998). While *Drosophila* expresses only one Fringe enzyme, there are three mammalian homologs (Lunatic Fringe, Manic Fringe and Radical Fringe) (Johnston et al. 1997). Fucose elongation by any of the three Fringes causes an increase in Notch signaling mediated by members of the Delta-like ligand (DLL) family, but can have variable effects on signaling initiated by the Jagged (JAG) family of ligands in mammals (LeBon et al. 2014; Kakuda and Haltiwanger 2017). These enzymes play extremely important roles in regulating Notch signaling throughout development. For instance, Lunatic Fringe is required for normal somitogenesis (Evrard et al. 1998; Zhang and Gridley 1998). Recent work has demonstrated that addition of GlcNAc by Fringe to Notch's extracellular domain creates a "Fringe-mediated Notch code," where modifications at specific EGF repeats can either enhance DLL-mediated signaling or inhibit JAG-mediated Notch signaling (Harvey et al. 2016; Kakuda and Haltiwanger 2017).

While POFUT1 is predicted to modify many other proteins based on consensus sequences, modification of most of these proteins has not been confirmed (Table I). Dysregulation of POFUT1 activity has, however, been shown to play an important role in several disorders and processes involving other proteins. Heterozygous mutations in POFUT1 have been associated with a rare dermatologic condition, Dowling-Degos disease, characterized by pigmentation abnormalities (Li et al. 2013; Chen et al. 2014). *O*-Fucosylation of EGF repeats also appears to play an important role in regulating the clustering of acetylcholine receptors by agrin (Kim et al. 2008). Amplification of POFUT1 has also been implicated as a prognostic marker and potential drug target for several cancer types including breast cancer (Milde-Langosch et al. 2014), oral squamous cell carcinoma (Yokota et al. 2013) and hepatocellular carcinoma (Sawey et al. 2011; Ma et al. 2016).

O-Fucosylation of TSRs

Like *Pofut1*, knockout of *Pofut2* in mice is embryonic lethal with severe defects in gastrulation, indicating its importance in development (Du et al. 2010). A recent report strongly suggests that ADAMTS9 is the target protein responsible for these defects, as knockout of *Adamts9* resulted in a phenotype essentially identical to *Pofut2* knockout (Benz et al. 2016). Other target proteins play an important role in regulating cell proliferation, migration and differentiation. *O*-Fucosylation of CCN1, which is required for its secretion, has been shown to be vital to these processes (Perbal 2004; Niwa et al. 2015). Additionally, members of the A Disintegrin and Metalloproteinase with ThromboSpondin motifs (ADAMTS) family of metalloproteinases play critical roles in mediating angiogenesis, extracellular structuring, inflammation and other developmental processes (Dubail and Apte 2015). Several proteins in this family also depend on *O*-fucosylation for their secretion (Ricketts et al. 2007; Wang et al. 2007; Vasudevan et al. 2015; Benz et al. 2016; Dubail et al. 2016). One of the affected proteins, ADAMTS13, is particularly noteworthy as its deficiency results in thrombotic thrombocytopenic purpura (TTP), a life threatening hematologic disorder (Ricketts et al. 2007). More work will be needed to determine the importance of *O*-fucosylation for processes mediated by other specific proteins.

O-Fucose residues on TSRs can be elongated with glucose by β3-glucosyltransferase (B3GLCT) (Figure 4B) further promoting secretion of target proteins. Mutations in this enzyme cause the human disease Peters plus syndrome, characterized by a number of defects in the eye chambers, limbs and intellectual development (Oberstein et al. 2006). Elimination of B3GLCT activity results in reduced secretion of some, but not all of the proteins regulated by POFUT2 modification (Vasudevan et al. 2015). A recent report from our lab suggests that the carbohydrate modifications added by POFUT2 and B3GLCT serve as a novel quality control system that recognizes and stabilizes properly folded TSRs. POFUT2 recognizes and sequentially fucosylates properly folded TSRs in the ER allowing B3GLCT to bind and add glucose to these TSRs. The data suggest that addition of these sugars stabilizes the folded form of the TSR, removing it from a folding cycle in the ER. Once all TSRs on a protein have been processed the protein can exit the ER (Vasudevan et al. 2015).

Fucose analogs

The development of chemically modified fucose analogs has revolutionized the study of fucose and fucosyltransferases by providing a valuable tool for modifying, tracking and inhibiting fucosylation of proteins. As early as 1992, it was recognized that the Lewis

Table I. List of putative human gene targets of POFUT1

Name and UNIPROT ID	Consensus/ total	Known human pathology (if any)
AGRIN (O00468)	2/4	Myasthenia, limb-girdle, familial (Huze et al. 2009; Maselli et al. 2012)
ATRAID (Q6UW56)	1/1	—
CD93 (Q9NYP3)	1/5	—
CD97 (P48960)	1/5	—
CELSR1 (Q9NYQ6)	2/8	Neural tube defects (Robinson et al. 2012)
CELSR2 (Q9HCU4)	2/7	—
CELSR3 (Q9NYQ7)	2/8	—
CFC1 (P0CG37)	1/1	Heterotaxy, visceral, 2, autosoma; transposition of the great arteries dextro-looped 2; Conotruncal heart malformations (Bamford et al. 2000; Goldmuntz et al. 2002)
CFC1B (P0CG36)	1/1	—
CNTNAP5 (Q8WYK1)	1/2	—
CRB1 (P82279)	8/19	Retinitis pigmentosa 12; Leber congenital amaurosis 8; Pigmented paravenouschorioretinal atrophy (den Hollander et al. 1999, 2001; McKay et al. 2005)
CRB2 (Q5IJ48)	8/15	—
CSPG2 (P13611)	2/2	Wagner vitreoretinopathy (Miyamoto et al. 2005; Kloeckener-Gruissem et al. 2013)
CUBN (O60494)	4/7	Recessive hereditary megaloblastic anemia 1 (Aminoff et al. 1999; Kristiansen et al. 2000)
DLK1 (P80370)	3/6	—
DLK2 (Q6UY11)	1/6	—
DLL1 (O00548)	4/8	—
DLL3 (Q9NYJ7)	2/6	Spondylocostaldysostosis 1, autosomal recessive (Bulman et al. 2000)
DLL4 (Q9NR61)	5/8	—
DNER (Q8NFT8)	6/10	—
EDIL3 (O43854)	1/3	—
EGF (P01133)	1/9	Hypomagnesemia 4 (Groenestege et al. 2007)
EGFL7 (Q9UHF1)	1/2	—
EGFLAM (Q63HQ2)	2/3	—
EMR1 (Q14246)	4/6	—
EMR2 (Q9UHX3)	1/5	—
EYS (Q5T1H1)	11/27	Retinitis pigmentosa 25 (Abd El-Aziz et al. 2008; Collin et al. 2008; Audo et al. 2010; Huang et al. 2010)
F7 (P08709)	1/2	Factor VII deficiency (O'Brien et al. 1991; Bernardi et al. 1994; Leonard et al. 1998; Girelli et al. 2000; Landau et al. 2009; Jiang et al. 2011)
F9 (P00740)	1/2	Hemophilia B; Thrombophilia, X-linked, due to factor IX defect (Green et al. 1989; Suehiro et al. 1989; de la Salle et al. 1993; Simioni et al. 2009)
F12 (P00748)	1/2	Factor XII deficiency; Hereditary angioedema 3 (Bernardi et al. 1987; Schloesser et al. 1995; Cichon et al. 2006; Dewald and Bork 2006)
FAT1 (Q14517)	2/5	—
FAT2 (Q9NYQ8)	1/2	—
FAT3 (Q8TDW7)	3/4	—
FAT4 (Q6V0I7)	5/6	Van Maldergem syndrome 2 (Cappello et al. 2013)
FBLN1 (P23142)	1/9	Complex type of synpolydactyly; associated with human breast cancer (Debeer et al. 2002; Greene et al. 2003)
FBLN7 (Q53RD9)	1/3	—
FBN2 (P35556)	1/47	Arthrogryposis, distal 9 (Putnam et al. 1995; Babcock et al. 1998; Park et al. 1998; Belleh et al. 2000; Gupta et al. 2002; Callewaert et al. 2009)
FBN3 (Q75N90)	1/44	—
HABP2 (Q14520)	1/3	—
HGFAC (Q04756)	2/2	—
JAG1 (P78504)	11/16	Alagille syndrome 1; Tetralogy of Fallot (Oda et al. 1997; Krantz et al. 1998; Eldadah et al. 2001)
JAG2 (Q9Y219)	9/16	—
LRP1 (Q07954)	5/22	—
LRP1B (Q9NZR2)	4/14	—
LTBP2 (Q14767)	1/20	Glaucoma 3, primary congenital, D; Microspherophakia and/or megalocornea, with ectopialentis and with or without secondary glaucoma; Weill-Marchesani syndrome 3 (Ali et al. 2009; Kumar et al. 2010; Haji-Seyed-Javadi et al. 2012)
MEGF6 (O75095)	1/27	—
MEGF8 (Q7Z7M0)	2/5	Carpenter syndrome 2 (Twigg et al. 2012)
MEGF10 (Q96KG7)	2/15	Myopathy, early-onset, areflexia, respiratory distress, and dysphagia (Logan et al. 2011; Boyden et al. 2012)
MEGF11 (A6BM72)	2/14	—
MMRN1 (Q13201)	1/1	Factor V Quebec (Hayward et al. 1996)
NCAN (O14594)	2/2	—

Continued

Table I. Continued

Name and UNIPROT ID	Consensus/ total	Known human pathology (if any)
NELL1 (Q92832)	1/5	—
NID2 (Q14112)	1/5	—
NOTCH1 (P46531)	20/36	Aortic valve disease 1 (Garg et al. 2005)
NOTCH2 (Q04721)	20/36	Alagille syndrome 2; Hajdu-Cheney syndrome (McDaniell et al. 2006; Isidor et al. 2011; Simpson et al. 2011)
NOTCH2NL (Q7Z3S9)	5/6	—
NOTCH3 (Q9UM47)	14/34	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy; Myofibromatosis, infantile 2 (Joutel et al. 1997; Dichgans et al. 1999; Fouillade et al. 2008; Martignetti et al. 2013)
NOTCH4 (Q99466)	18/29	—
PAMR1 (Q6UXH9)	1/1	—
PEAR1 (Q5VY43)	1/9	—
PGBM (P98160)	3/4	Schwartz-Jampel syndrome; Dyssegmental dysplasia Silverman-Handmaker type (Nicole et al. 2000; Arikawa-Hirasawa et al. 2001)
PGCB (Q96GW7)	1/1	—
PROC (P04070)	1/2	Thrombophilia due to protein C deficiency, autosomal dominant and autosomal recessive (Romeo et al. 1987; Miyata et al. 1995; Couture et al. 1998)
PROZ (P22891)	1/2	—
RELN (P78509)	2/8	Lissencephaly 2 (Hong et al. 2000)
SLIT1 (O75093)	2/9	—
SLIT2 (O94813)	3/7	—
SLIT3 (O75094)	3/9	—
SNED1 (Q8TER0)	10/15	—
SREC2 (Q96GP6)	1/7	Van den Ende-Gupta syndrome (Anastasio et al. 2010)
STAB1 (Q9NY15)	3/16	—
STAB2 (Q8WWQ8)	6/17	—
SUSD1 (Q6UWL2)	2/3	—
SVEP1 (Q4LDE5)	4/9	—
TEN1 (Q9UKZ4)	1/8	—
TEN2 (Q9NT68)	2/8	—
TEN4 (Q6N022)	2/8	—
TIE1 (P35590)	1/3	—
TPA (P00750)	1/1	Increased activity results in excessive bleeding; Defective release results in thrombosis or embolism (Degen et al. 1986).
TSP3 (P49746)	1/3	—
UMOD (P07911)	3/3	Familial juvenile hyperuricemic nephropathy 1; Medullary cystic kidney disease 2; Glomerulocystic kidney disease with hyperuricemia and isosthenuria (Hart et al. 2002; Rampoldi et al. 2003)
UMODL1 (Q5DID0)	1/3	—
UROK (P00749)	1/1	Quebec platelet disorder (Paterson et al. 2010)
VASN (Q6EMK4)	1/1	—
VWA2 (Q5GFL6)	2/2	—
VWDE (Q8N2E2)	3/7	—
WIF1 (Q9Y5W5)	2/5	—

Potential targets of POFUT1 are listed based on a ScanProsite database search of all human proteins containing EGF repeats that contain the $C^2XXXX(S/T)C^3$ consensus sequence for *O*-fucosylation cross-referenced with the Uniprot database. Splice variants were not considered. The number of EGF repeats containing the consensus sequence/total number of EGF domains is listed, as well as any known human pathologies associated with the putative targets. Confirmed POFUT1 targets are listed in boldface.

fucosyltransferase could tolerate GDP-fucose modified at the C-6 position by even a large addition, and that this could be used as a powerful tool for labeling lipids and proteins that incorporated this modified form of fucose (Srivastava et al. 1992). Taking advantage of this enzymatic promiscuity, researchers have developed strategies to use fucose analogs with an azide or alkyne group at the C-6 position to metabolically incorporate fucose analogs producing labeled fucosylated glycoproteins. Once incorporated into target proteins, "click"-chemistry can be used to attach fluorophores or other groups to the fucose analog. This strategy has allowed for successful *in vivo* imaging of fucose in several model organisms (Laughlin et al. 2008; Laughlin and Bertozzi 2009), plants (Anderson et al. 2012) and cell cultures (Sawa et al. 2006; Hsu et al. 2007). Others have used this strategy to tag fucosylated proteins with biotin allowing for their identification using anti-biotin or streptavidin probes for detection by Western blot or isolation using a streptavidin pulldown (Liu et al. 2012; Al-Shareffi et al. 2013), potentially allowing for the identification of unknown fucosylated glycoproteins. These tools continue to develop, as one group recently showed that 7-alkynyl fucose is more efficiently utilized by FUT8 than 6-alkynyl fucose (Kizuka et al. 2016). This type of development could ultimately allow for more efficient and/or targeted labeling of glycoproteins.

In addition to their utility for identifying and tracking fucosylated proteins, fucose analogs have also been investigated as potential inhibitors of fucosyltransferases. Monosaccharide analogs have

Table II. List of putative human gene targets of POFUT2

Name and UNIPROT ID	Consensus/total	Known human pathology (if any)
ADAMTS1 (Q9UHI8)	3/3	—
ADAMTS2 (O95450)	2/4	Ehlers-Danlos syndrome 7 C (Colige et al. 1999)
ADAMTS3 (O15072)	2/4	—
ADAMTS4 (O75173)	1/1	—
ADAMTS5 (Q9UNA0)	2/2	—
ADAMTS6 (Q9UKP5)	3/5	—
ADAMTS7 (Q9UKP4)	5/8	—
ADAMTS8 (Q9UP79)	2/2	—
ADAMTS9 (Q9P2N4)	12/15	—
ADAMTS10 (Q9H324)	3/5	Weill-Marchesani syndrome 1 (Dagoneau et al. 2004; Kutz et al. 2008)
ADAMTS12 (P58397)	6/8	—
ADAMTS13 (Q76LX8)	7/8	TTP, congenital (Levy et al. 2001; Kokame et al. 2002; Antoine et al. 2003; Schneppenheim et al. 2003; Ricketts et al. 2007)
ADAMTS14 (Q8WXS8)	2/4	—
ADAMTS15 (Q8TE58)	3/3	—
ADAMTS16 (Q8TE57)	6/6	—
ADAMTS17 (Q8TE56)	4/5	Weill-Marchesani-like syndrome (Morales et al. 2009)
ADAMTS18 (Q8TE60)	4/5	Microcornea, myopic chorioretinal atrophy, and telecanthus (Aldahmesh et al. 2013)
ADAMTS19 (Q8TE59)	4/5	—
ADAMTS20 (P59510)	11/15	—
ADAMTSL1 (Q8N6G6)	8/9	—
ADAMTSL2 (Q86TH1)	6/7	Geleophysic dysplasia 1 (Le Goff et al. 2008)
ADAMTSL3 (P82987)	8/10	—
ADAMTSL4 (Q6UY14)	2/6	Ectopialentis 2, isolated (Ahram et al. 2009); Ectopialentis et pupillae (Christensen et al. 2010)
ADAMTSL5 (Q6ZMM2)	1/1	—
BAI1 (O14514)	4/5	—
BAI2 (O60241)	4/4	—
BAI3 (O60242)	4/4	—
C-6 (P13671)	1/3	Complement component 6 deficiency (Ikinciogullari et al. 2005)
CILP2 (Q8IUL8)	1/1	—
CTGF (P29279)	1/1	—
CYR61 (O0062)	1/1	—
HMCN1 (Q96RW7)	6/6	Age-related macular degeneration 1 (Schultz et al. 2003)
ISM1 (B1AKI9)	1/1	—
NOV (P48745)	1/1	—
PPN (O95428)	4/5	—
PROP (P27918)	4/7	Properdin deficiency (Fredrikson et al. 1996; Fredrikson et al. 1998; van den Bogaard et al. 2000)
SEM5A (Q13591)	2/7	—
SEM5B (Q9P283)	2/5	—
SPON1 (Q9HCB6)	5/6	—
SSPO (A2VEC9)	10/24	—
THS7A (Q9UPZ6)	4/15	—
THS7B (Q9C0I4)	4/18	—
THSD1 (Q9NS62)	1/1	—
THSD4 (Q6ZMP0)	3/6	—
TSP1 (P07996)	3/3	—
TSP2 (P35442)	3/3	Intervertebral disc disease (Hirose et al. 2008)
WISP1 (O95388)	1/1	—
WISP2 (O76076)	1/1	—
WISP3 (O95389)	1/1	Progressive pseudorheumatoidarthropathy of childhood (Hurvitz et al. 1999)

Potential targets of POFUT2 are listed based on a ScanProsite database search of all human proteins containing TSRs that also contain the CX_{2-3}(S/T)C consensus sequence for *O*-fucosylation cross-referenced with the Uniprot database. Splice variants were not considered. The number of TSRs containing the consensus sequence/total number of TSR domains is listed, as well as any known human pathologies associated with the putative targets. Confirmed POFUT2 targets are indicated in boldface.

already been approved for the treatment of lysosomal storage disorders, diabetes and are being developed for potential use in other diseases (Gloster and Vocadlo 2012). As discussed above, fucose plays an important role in many cancer types and other disorders, so the development of fucosyltransferase inhibitors might serve as a valuable clinical tool. Several groups have begun screening and developing inhibitors toward this end (Fuster and Esko 2005; Hosoguchi et al. 2010; Rillahan et al. 2011; Dalziel et al. 2014). One group used click chemistry to generate fucose analogs with a variety of different groups and screened them as potential

fucosyltransferase inhibitors, identifying several candidates (Lee et al. 2003). Fucose analogs that inhibit transfer of fucose by several fucosyltransferases including FUT4, FUT7 and FUT8 can be used to prevent selectin-mediated cell migration, a process that plays an important role in cancer metastasis (Rillahan et al. 2012; Villalobos et al. 2015). These fucose analog inhibitors are orally active and slow tumor cell proliferation in mice (Okeley et al. 2013). Additionally, taking advantage of the role fucosylation plays in regulating learning and memory, fucose analogs have been used to cause reversible amnesia and inhibition of long-term memory formation (Rose and Jork 1987; Krug et al. 1991; Lorenzini et al. 1997).

In addition to their use as fucosyltransferase inhibitors, fucose analogs that are tolerated by fucosyltransferases can be incorporated into target proteins and potentially alter protein behavior. For example, fucose analogs that are efficiently utilized by POFUT1 (Al-Shareffi et al. 2013) can be used to alter Notch signaling. Notch receptors are a major POFUT1 target, as discussed above, and can be activated by two different ligand families: DLL and JAG ligands. Modification of attached fucose residues at the 6-carbon with alkyne or alkene groups causes an inhibition of Notch activation that preferentially affects DLLs (Schneider et al. In Review). This ability to discriminate between ligands provides a potentially very useful tool for evaluating Notch signaling. Similar strategies might be developed into targeted therapeutics for disease.

Funding

Original work was supported by NIH grant GM061126.

Acknowledgements

We would like to thank Drs Pamela Stanley, Hideyuki Takeuchi and Shinako Kakuda for their helpful comments and suggestions.

Conflict of interest statement

None declared.

Abbreviations

ADAMTS	A Disintegrin and Metalloproteinase with ThromboSpondin motifs
ADCC	Antibody dependent cellular cytotoxicity
AFP	α-Fetoprotein
B3GLCT	β3-glucosyltransferase
BPH	Benign prostatic hyperplasia
CLL	Chronic lymphocytic leukemia
DLL	Delta-like ligand
EGF	Epidermal growth factor-like
FUT	Fucosyltransferase
FX protein	GDP-keto-6-deoxymannose 3,5 epimerase
GalNAc	*N*-acetylgalactosamine
GlcNAc	*N*-acetylglucosamine
JAG	Jagged
LAD2	Leukocyte adhesion deficiency II
LTP	Long-term potentiation
mAb	Monoclonal antibody
POFUT	Protein *O*-fucosyltransferase
PPS	Peters Plus Syndrome
PSA	Prostate-specific antigen
RBC	Red blood cell
TSR	Thrombospondin type 1 repeat
TTP	Thrombotic thrombocytopenic purpura

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