Glycoconj J (2013) 30:5–10
DOI 10.1007/s10719-012-9375-4

Developmental diseases caused by impaired nucleotide sugar transporters

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Received: 24 February 2012 / Accepted: 28 March 2012 / Published online: 17 April 2012

Abstract Nucleotide sugar transporters play critical roles in glycosylation of proteins, lipids and proteoglycans, which are essential for organogenesis, development, mammalian cellular immunity and pathogenicity of human pathogenic agents. Functional deficiencies of these transporters result in global defects of glycoconjugates, which in turn lead to a diversity of biochemical, physiological and pathological phenotypes. In this short review, we will highlight human and bovine diseases caused by mutations of these transporters.

Keywords Nucleotide sugar transporter · Glycosylation · Development · Diseases · Pathogenicity

Abbreviations

UDP-GlcA	uridine diphosphate glucuronic acid
UDP-GlcNAc	uridine diphosphate-*N*-acetylglucosamine
UDP-GalNAc	uridine diphosphate-*N*-acetylgalactosamine
GDP-Fuc	guanosine diphosphate fucose
GDP-Man	guanosine diphosphate mannose
CMP-SA	cytidine monophosphate sialic acid
LAD II	leukocyte adhesion deficiency II
ER	endoplasmic reticulum

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Introduction

Nucleotide sugars are transported by specific transporters from the cytosol, their site of synthesis, into the lumen of Golgi apparatus or endoplasmic reticulum (ER), where they serve as substrates for glycosylation reactions. Given their essential roles in the biosynthesis of glycoproteins, glycolipids and proteoglycans it is not surprising that these transporters have been identified in all eukaryotes examined so far. Their biochemical characteristics and biological significance have been demonstrated in mammals, *Caenorhabditis elegans*, *Drosophila melanogaster*, yeast, fungi, *Leishmania, Entamoeba* [1, 2] and recently *Trypanosoma brucei* (unpublished results). Importantly, mutations in these transporters, as will be discussed below, result in human diseases such as leukocyte adhesion deficiency II and Schneckenbecken dysplasia as well as complex vertebral malformation in bovines.

Over the past years, numerous biochemical studies have demonstrated that glycoconjugates were deficient in the particular sugar for which the corresponding nucleotide sugar transport was defective [1, 2]. However, our recent studies of silencing nucleotide sugar transporter genes of mammalian cells showed a more global defect in the synthesis and secretion of not only glycoproteins, but also in non glycoproteins. The latter is probably the result of ER stress induction and protein translation inhibition and may explain the diverse symptoms in mammalian diseases caused by transporter mutations. Further in depth studies of transporter structures, functions and their regulation of glycosylation in mammals should lead to a better understanding of the molecular mechanisms underlying the above diseases and facilitate the discovery of appropriate therapies.

General properties of nucleotide sugar transporters

These transporters, which have been characterized at a molecular level mainly in the Golgi apparatus, are hydrophobic, polytopic proteins that cross the Golgi apparatus membrane 6–10 times. An even number of spanning domains allows both the amino and carboxyl termini to face the cytosolic side of the Golgi apparatus (Fig. 1). Biochemical analyses with proteases show that the cytosolic side of a transporter protein is essential for substrate recognition and transport [3–5]. This property might be used for designing transporter inhibitors specific to human pathogenic agents.

All nucleotide sugar transporters identified so far have similar length (300–350 amino acids) and molecular weight (35–45 kDa). They function, in most cases, as homodimers in the membrane but apparently as a hexamer in the *Leishmania* GDP-mannose transporter [6]. Sequence alignment analyses and experimental evidence showed no direct correlation between primary amino acid sequence and substrate specificity, *e.g.* transporters sharing little amino acid sequence identity (20–22 %) may have the same substrate specificity, whereas transporters sharing greater sequence identity (45–50 %) may have different substrate specificities. Therefore, one should be aware that many designated substrate specificities in genome databases might be incorrect.

As Golgi apparatus targeting signals of transporter proteins are conserved across species, a predicted transporter from a given genome can be characterized by heterologous expression of the tagged-coding sequence followed by *in vitro* biochemical transport assays and/or *in vivo* genetic complementation of mutants defective in activity of known transporters.

Biochemical characteristics of nucleotide sugar transport

Using Golgi apparatus vesicles and reconstituted proteoliposomes, transport of the entire nucleotide sugar molecule into the lumen of organelles was found to be saturable with Kms in the range of 1–30 micromolar. Further studies indicated that the nucleotide, but not the sugar, plays an important role in recognition and binding to the nucleotide sugar transporter. Evidence supporting this is that transport of a nucleotide sugar is competitively inhibited by the corresponding nucleoside mono- or di-phosphate, but not by free sugars. However the sugar bound to the nucleoside phosphate determines transport specificity [7, 8]. A specific transporter can transport a single or multiple nucleotide sugar substrates. Up to now, no transporters that recognize pyrimidine sugars (*i.e.* UDP-sugars) have been found to transport purine sugars (*i.e.* GDP-sugars) and *vice versa*. However, recent studies with *Trypanosoma brucei*

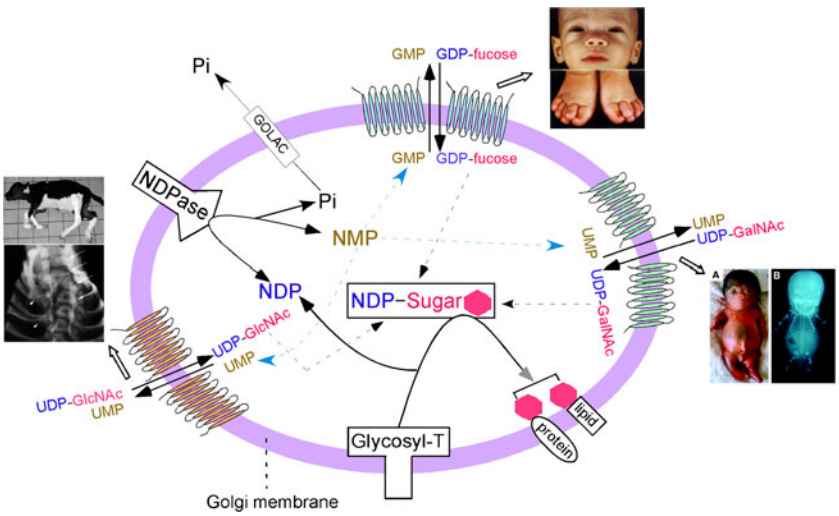

Fig. 1 The Golgi apparatus nucleoside diphosphate sugar transport/antiport cycle and diseases thereof. Guanosine 5′-diphosphate fucose (GDP-fucose), uridine 5′- diphosphate-*N*-acetylglucosamine (UDP-GlcNAc) and uridine 5′-diphosphate *N*-acetylgalactosamine (UDP-GalNAc) are transported from the cytosol into the Golgi apparatus lumen where glycosyltransferases transfer the sugars to glycoproteins and glycolipids. The other reaction products, nucleoside 5′-diphosphates (UDP and GDP) are converted by a luminal nucleoside 5′-diphosphatase to nucleoside 5′-monophosphates (UMP and GMP), which exit the lumen of the Golgi apparatus *via* their corresponding nucleotide sugar antiporters. The other reaction product of the nucleoside diphosphatase, inorganic phosphate, exits the lumen *via* the GOLAC transporter. Two human diseases: leukocyte adhesion deficiency syndrome II (resulting from mutations in GDP-fucose transporter) [24–27] and Schneckenbecken syndrome (resulting from mutations in UDP-GalNAc/UDP-glucuronic acid transporter) [35] are shown. Complex vertebral malformation, a disease resulting from a mutation of the UDP-GlcNAc transporter has been described in bovines [36]

transporters have shown transport of both UDP- and GDP-sugars by a single transporter (unpublished results). Transport of multiple substrates can be competitive, *i.e.* transport of one substrate inhibits transport of another substrate(s); or simultaneous and independent [9] where one substrate does not inhibit entry of another. The molecular mechanisms for this remain to be investigated.

The Golgi apparatus nucleotide sugar transport/nucleoside monophosphate antiport cycle and its regulatory role in glycosylation and development

Nucleotide sugar transporters are antiporters with the corresponding nucleoside monophosphates, *i.e.* entry of nucleoside diphosphate-sugar into the Golgi lumen is coupled to exit from the Golgi lumen of the corresponding nucleoside monophosphate (Fig. 1) [10, 11].

The nucleotide sugar transport/antiport cycle regulates glycosylation by providing sugar donors for glycosyltransferases, which catalyze the transfer of the sugars to macromolecular acceptors. Loss of function mutations in the transporter/antiporter cycle cause glycosylation and developmental defects. Diseases caused by mutations in mammals will be discussed below. Mutations in a *C. elegans* multisubstrate transporter, SQV-7, caused defects in the biosynthesis of glycosaminoglycans resulting in aberrant embryogenesis and vulval epithelial invagination [12, 13]. Mutations in a *Drosophila melanogaster* multisubstrate nucleotide sugar transporter, *fringe connection* (*frc*), caused defects in the biosynthesis of the Notch receptors leading to aberrant wing and limbs [14, 15]. Studies of a multisubstrate nucleotide sugar transporter knockout of the protozoan parasites, *Leishmania donovani* and *Leishmania major*, showed a global deficiency of phosphoglycan-containing molecules and loss of infectivity [16–18]. However, loss of infectivity did not occur in a knockout of *Leishmania mexicana* [19].

Glycosylation is also regulated by the generation of transporters' antiport products, nucleoside monophosphates (Fig. 1). The important roles of nucleoside diphosphatases (NDPases), which are responsible for producing antiport products, in glycosylation and morphogenesis were demonstrated, initially in yeast [20, 21]) and later in *C. elegans*. Mutations in the *C. elegans'* NDPase, *mig-23*, caused a defect in glycosylation of the MIG-17 protease, leading to aberrant gonad morphology [22]. Consistent with this, RNAi depletion of another NDPase of *C. elegans,* APY-1, caused altered pharynx morphology and activated the unfolded protein response probably as a consequence of defects in *N*-linked glycosylation [23].

Mammalian diseases resulting from mutations in nucleotide sugar transporters

Leukocyte adhesion deficiency syndrome II, resulting from mutations in the human GDP-fucose transporter

The GDP-fucose transporter plays important roles in various physiological processes such as growth, development and cellular immunity by regulating fucosylation of glycoproteins and proteoglycans. Among these are the Notch receptor, heparan sulfate and selectin ligands involved in leukocyte adhesion and defense of bacterial infections. Mutations in the GDP-fucose transporter (SLC35C1) resulted in a global defect in fucosylation leading to leukocyte adhesion deficiency syndrome II (LAD II) also called Congenital Disorder of Glycosylation (CDG) IIc [24–26]. This is an autosomal recessive disorder characterized by severe mental and growth retardation and other neurological manifestations. Patients show a flat face with a depressed nasal bridge, antiverted nostrils, abnormal toes and aberrant skeleton (Fig. 1) [27]. LAD II patients have a broad deficiency in the expression of fucose-containing cell surface glycoconjugates including ABH, Lewis^a and Lewis^b blood group antigens, the Lewis^x antigen or CD15, and the sialyl Lewis^x antigen or CD15s, the latter implicated in the leukocyte selectin adhesion system. Patients have the rare blood group called Bombay, a deficiency in Fucα1-2Gal linkage of the H antigen on the red cell surface [28].

LADII patients have recurrent severe infections suggesting immunodeficiency. The underlying molecular defect was found to be a lack of the fucose-containing tetra saccharide "sialyl Lewis ^{X}", a ligand for selectins on the patient's leukocyte surface. Under normal physiological conditions, interaction of sialyl Lewis ^{X} with the lectin domain of endothelial surface selectins mediates leukocyte rolling and adhesion. This is an essential step in the recruitment of neutrophils to inflammation sites [27, 29]. Lack of sialyl Lewis ^{X} resulted in neutrophils defective in adhesion and motility leading to leukocytes unable to traffic to inflammatory sites. Detailed analyses of glycan structures from fibroblasts derived from LAD II patients showed a severely reduced synthesis of *N*-, but not *O*-linked glycans [30], while the corresponding fucosyltransferase activities responsible for the synthesis of both these structures were normal [29]. Dietary fucose supplementation of some patients was shown to reduce the incidence and severity of infections and partially improve their neurological symptoms. However, patients carrying other mutations were not responsive to oral fucose therapy [31, 32]. The reason for this difference is not clear.

Similar to human GDP-fucose transporter mutations, knockout of the corresponding transporter gene in mice resulted in a broad fucosylation defect. The transporter-

null mice exhibited many phenotypic characteristics found in LADII patients such as growth retardation and impaired leukocyte adhesion function [33]. Interestingly, hypofucosylation in cell lines derived from GDP-fucose transporter knockout mice can also be reversed by addition of fucose to the culture medium. One of the mechanistic possibilities is that high concentration of free fucose may lead to increase of GDP-fucose synthesis, which may overcome the consequences of a low affinity mutant transporter for its substrate.

Schneckenbecken dysplasia, resulting from mutations in the UDP-*N*-acetylgalactosamine/glucuronic acid transporter

A UDP-GalNAc/UDP-GlcA transporter (SLC35D1) [34] plays an essential role in human chondrogenesis and skeletal development. Mutations in this transporter caused human Schneckenbecken dysplasia, which is an autosomal recessive, perinatally lethal, skeletal dysplasia. The patient has small-stature with short-limbs, narrow thorax, and a protuberant abdomen (Fig. 1). The German term 'Schneckenbecken' is derived from the distinctive snail-like appearance present in both iliac wings. Radiographs revealed a narrow chest and scoliosis (which also occurs in a UDP-GlcNAc transport-deficient cattle disease, complex vertebral malformation shown in Fig. 1 and discussed below). Chondroitin sulfate chain length and content are essential for cartilage growth activity, particularly for epiphyseal cartilage formation. The severe chondrodysplasia caused by mutations of transporter SLC35D1 demonstrated its crucial role in cartilage formation by providing UDP-GalNAc and UDP-GlcA used as sugar donors for the biosynthesis of chondroitin sulfate. The defect, which is confined to cartilage, may be explained by the particularly high rate of chondroitin sulfate synthesis in chondrocytes, and thus the high requirements for transport of these two nucleotide sugar substrates.

The essential roles of the UDP-GalNAc/UDP-GlcA transporter in chondroitin sulfate biosynthesis and skeletal development have been shown by the deletion of the mouse *SLC35D1* transporter gene, which shares 97 % amino acid sequence identity with its human counterpart. Knockout of this transporter in mice resulted in neonatal death with severe developmental defects in cartilage and skeleton. Similar to human Schneckenbecken dysplasia described above, *Slc35d1*-null mice exhibited dwarfism, narrow thorax, protruding abdomen and severe short limbs. Histological analyses of epiphyseal cartilage showed a greatly reduced and disorganized proliferating zone with closely packed round chondrocytes, instead of normal columnar alignment of chondrocytes. Detailed immunofluorescence and biochemical studies confirmed that both the number and length of chondroitin sulfate chains, but not heparan sulfate chains, were significantly reduced in *Slc35d1*-deficient mice in agreement with a possible defect in chondroitin sulfate biosynthesis [35].

As SLC35D1 mutations were only found in Schneckenbecken dysplasia, but not in other type of spondylodysplastic dysplasia diseases [35], searching for the mutations in these patients may lead to the identification of new causative genes functioning in the same genetic pathway, possibly other nucleotide sugar transporters responsible for skeletal dysplasia. Indeed, a missense mutation in the bovine *SLC35A3* gene, which encodes a UDP-GlcNAc transporter, is known to be responsible for complex vertebral malformation (discussed below) [36].

A human congenital disorder of glycosylation type IIf, resulting from mutations in the Golgi CMP-sialic acid transporter

A patient with mutations in the CMP-sialic acid transporter gene (*SLC35A1*) leading to CDG IIf has been described. The patient displayed respiratory distress syndrome, severe cutaneous hemorrhages (due to thrombocytopenia) and infections (due to neutropenia and a complete lack of the sialyl Lewis^X antigen on leukocytes). Platelet analyses showed a reduction in GPIb, a sialic acid-containing glycoprotein important for platelet adhesion to sub endothelium [37]. Functions of leukocytes and platelets were mostly affected possibly because of high sialylation on the surface of these cells. Two mutated alleles from the patient's leukocytes were characterized by genetic complementation of CHO Lec2 mutant cells deficient in CMP-sialic acid transport [38]. Neither of the two patient alleles restored the asialo surface phenotype of Lec2 cells suggesting that both mutations are loss-of-function mutations [39].

Complex vertebral malformation: a cattle disease resulting from a mutation in the UDP-*N*-acetylglucosamine transporter

Complex vertebral malformation is a congenital recessive disease of cattle, characterized by fused and misshaped vertebrae, scoliosis (Fig. 1) and cardiac abnormalies. The disease eventually causes fetuses to be aborted or perinatal death [40]. The causative genetic defect was shown to be a single missense mutation (V180F) in the UDP-GlcNAc transporter gene (*SLC35A3*). While the wild-type bovine gene complemented the corresponding *K. lactis* mutant strain [40, 41], the mutated gene did not. Proteomic analyses showed an asparagine *N*-linked glycosylation defect in cardiac and skeletal muscle tissues of mutant animals [36]. Studies of 27 patients with radiographic evidence of vertebral malformation have so far failed to show mutations in the above transporter gene [42].

Concluding remarks

Over the past decade, numerous nucleotide sugar transporters have been identified in a wide variety of species. Although progress has been made in understanding the biochemical properties, biological functions and implications in development and diseases of these transporters, knowledge is missing regarding their functional spatial structures and interactions (genetically or physically) with glycosyltransferases and NDPases involved in the transport/antiport cycle. Causal relationships between impaired transporter functions and complex clinical symptoms remain poorly understood. Our recent findings, that silencing these transporters in mammalian cells results in a general inhibition of synthesis and secretion of glyco- and nonglycoproteins, ER stress and ablated protein translation initiation, raise important questions regarding the mechanism for this as well as understanding the phenotypes at the molecular level of the above described diseases, which may be more complex than thought up to now.

Efforts should be made toward understanding and combating these transporter diseases. 1. Early diagnosis of mutations in the genes for which transporter diseases have been identified is now possible. 2. The cellular glycosylation patterns associated with pathological changes in transporter-deficient patients should be further investigated. 3. Dietary sugar supplementation should be further studied as it is associated with certain transporter diseases. 4. Gene therapy for transporter diseases will be one of the future directions to pursue. 5. Finally, the design and development of specific inhibitors of nucleotide sugar transport may be beneficial in the treatment of infectious diseases caused by pathogenic lower eukaryotes. Because transport of some nucleotide sugars occurs only in some lower eukaryotes but not in humans or other mammals (*e.g.* GDP-mannose transport), inhibition of these transporters should hold promise for a pathogen-specific therapy, while being harmless to their mammalian hosts.

Acknowledgements We thank Drs. Phillips W. Robbins and David E. Levin for helpful comments on the manuscript. Work in the authors' laboratory was supported by National Institutes of Health grant GM-30365.

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