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O-Mannosylation and Human Disease

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Abstract

Glycosylation of proteins is arguably the most prevalent co- and post-translational modification. It is responsible for increased heterogeneity and functional diversity of proteins. Here we discuss the importance of one type of glycosylation, specifically O-mannosylation and its relationship with a number of human diseases. The most widely studied O-mannose modified protein is alpha-dystroglycan (α -DG). Recent studies have focused intensely on α -DG due to the severity of diseases associated with its improper glycosylation. O-mannosylation of α -DG is involved in cancer metastasis, arenavirus entry, and multiple forms of congenital muscular dystrophy (1, 2). In this review, we discuss structural and functional characteristics of O-mannose initiated glycan structures on α -DG, enzymes involved in the O-mannosylation pathway, and the diseases that are a direct result of disruptions within this pathway.

Keywords

Alpha-dystroglycan; arenavirus; cancer; LARGE; ISPD; metastasis; congenital muscular dystrophy; dystroglycanopathy

Introduction

O-mannosyl glycans were first reported on mammalian proteins over 30 years ago, when analyzing a proteoglycan enriched fraction of brain lysate (3). One of the most predominant O-mannosyl glycan structures observed is the O-mannosyl tetrasaccharide (Sia α 3Gal β 4GlcNAc β 2Man α -Ser/Thr), which was first identified on α -DG purified from bovine peripheral nerve tissue (4). α -DG is an integral glycoprotein of the dystrophin-glycoprotein complex (DGC) that serves to connect the actin cytoskeleton with the extracellular matrix (Fig. 1) by interacting with ECM proteins such as laminin in a glycosylation dependent manner (5, 6). Disruptions in the O-mannosylation pathway that lead to hypoglycosylation of α -DG are causative for several forms of congenital muscular dystrophy, and promote metastasis of many cancerous cell lines (7, 8). In addition to binding to proteins of the ECM, α -DG is a cell surface receptor for several arenaviruses that bind specifically to O-mannosyl structures to facilitate entry into the host cell (9-11).

Dystroglycan

Dystroglycan, or Cranin as it was originally named, was first identified over two decades ago when isolated from embryonic chicken brains (12). DG is widely expressed among all tissue types but is more prevalent in skeletal muscle and brain. The dystroglycan gene, DAG1, encodes a single polypeptide that is later post-translationally cleaved into two non-

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covalently bound subunits α - and β -dystroglycan (α -DG and β -DG) (13). The β -subunit is a transmembrane protein that interacts with dystrophin and utrophin serving to connect the extracellular protein, α -DG to the actin cytoskeleton (13, 14). α -DG is an extensively O-glycosylated membrane protein that is predicted to have a molecular weight of ~ 72 kDa. However, due to extensive glycosylation, α -DG is more commonly observed as a diffuse set of bands ranging from 150-200 kDa when separated by SDS-PAGE (13).

Several groups have identified both O-GalNAc and O-mannose initiated glycan structures within the mucin region of α -DG (4, 15-18). Several groups have worked towards mapping sites of glycosylation within the mucin region of skeletal muscle α -DG, identifying multiple sites of modification (15, 18, 19). Additionally, to aid in mapping sites of O-mannosylation, an amino acid consensus sequence has been proposed based upon *in vitro* experiments (20). However, this sequence does not appear to be in perfect agreement with *in vivo* experiments (15, 18, 19). Classical O-mannosyl glycan structures on α -DG were thought to be necessary for α -DG to bind to extracellular ligands such as laminin, agrin, and perlecan (2, 21, 22). However, the ability of α -DG to bind to laminin is not solely dependent upon the presence of the classic O-mannosyl tetrasaccharide, as trimming of O-mannosyl glycan structures with glycosidases has been shown to increase the ability of α -DG to bind laminin (23).

Recently, a novel O-mannosyl glycan structure (GalNAc β 3GlcNAc β 4Man) was identified within the mucin region of α -DG, in which the initiating mannose residue is extended at the 6 position by a phosphate in a phosphodiester linkage (17). The phosphate group is modified by an unknown moiety "X" that is deemed necessary for α -DG to bind laminin (17). Further, the pphosphorylated O-Man was seen to be extended in a 1,4 linkage, as opposed to 1,2, by a GlcNAc followed by 1,3 capping with a GalNAc residue (Fig. 2). Treatment of α -DG with aqueous hydrofluoric acid (HFAq), which cleaves the phosphodiester linkage, results in a shift from 150 to 70 kDa by western blot analysis, loss of reactivity with the IIIH6 antibody that recognizes functional α -DG, and loss of laminin binding (17). This suggests that the "X" moiety is the necessary structure mediating α -DG receptor function and that the modification is of substantial molecular weight and/or highly negatively charged. The "X" modification has also been shown to be dependent on the activity of the glycosyltransferase Like-acetylglucosaminyltransferase (LARGE) (24-27). More recent studies have demonstrated that LARGE produces a polysaccharide with repeating units of [-3Xyl- α 1,3 GlcA β 1-]. This group has also shown that the xylosyl- and glucuronyltransferase activities of LARGE are required for α -DG to bind laminin and other ECM ligands (28). This indicates that the "X" modification, at least in part, consists of this newly discovered repeating disaccharide though it remains to be determined where and how this repeating disaccharide is attached to glycans on α -DG.

Highlighting the importance of dystroglycan, null mice such as the DAG1^{-/-} knockout mouse are early embryonic lethal (29, 30). One such group of mice was shown to cease development at day 6.5 with failure to progress in development after a severe perturbation in basement membrane formation (31). The embryonic lethality of a completely DG-null mouse underscores the fundamental importance of DG in basic cellular structure and function. Surprisingly, chimeric mice develop normal basement membranes and exhibit only a mild phenotype of MD (29-31).

Dystroglycanopathies and Implicated Genes

Muscular dystrophy (MD) is an assorted collection of recessive genetic illnesses defined by the consecutive onset of weakness and wasting of skeletal muscle (32, 33). Charles Bell is accredited with the first account of identifying the disease in 1830 as an affliction in boys that caused progressive weakness, and later Guillaume Duchenne gave a comprehensive

account of a severe form, that now carries his name. Duchenne's MD is linked to mutations within dystrophin and accounts for approximately 95% of Muscular dystrophy cases. Further examination has successfully subdivided MD into multiple disease groups based primarily on the source of the affliction. Aberrant glycosylation of α -DG has been associated with numerous forms of muscular dystrophy that have been dubbed the Dystroglycanopathies. This large subset of Congenital Muscular Dystrophy (CMD) range in phenotype, from mild muscle wasting and basement membrane separation to severe muscle wasting and mental retardation (the latter being a highly penetrant feature of CMD (5, 34)). Mutations in known and putative glycosyltransferases that have been associated with defects in proper glycosylation of α -DG include POMT1, POMT2, POMGnT1, LARGE, Fukutin, Fukutin related protein and ISPD (Table 1) (26, 35-39). The fact that different mutations in the same gene can cause dystrophies of differing severity strongly argues that many of the mutations are hypomorphic in nature. Nearly half of the patients suffering from a dystroglycanopathy have no identifiable mutation in the seven known causative genes. Recently, a mutation in the DAG1 gene itself was found that caused CMD (40). The newest identified causative gene, ISPD, was determined through complementation assays and alternately through genetic screening and may account for nearly half of the WWS diagnoses (38, 39). However, this still leaves many genetic mutations unidentified. The full elucidation of the functional glycan structures and the enzymes responsible for the synthesis will likely lead to the identification of other causal genes.

POMT1/POMT2

Protein O-mannosyltransferase 1 (POMT1, OMIM 607243) is the first protein involved in the mammalian O-mannosylation pathway. POMT1 and POMT2 (OMIM 607439), a closely related protein, are type III transmembrane glycosyltransferases that co-localize in the endoplasmic reticulum. Together they catalyze the O-linked addition of a mannose from a dolichol-linked precursor onto a serine or threonine residue of a polypeptide (41-43). Expression of both appears to be a prerequisite for normal enzymatic structure and function, and mutations in either gene produce very similar (and often severe) phenotypes. Of all diseases with molecular foundations in the mutation of POMT1, Walker-Warburg syndrome (WWS, OMIM 236670) is the most commonly observed. WWS is a recessive disorder that presents with a severely affected physiological and anatomical phenotype, including type II lissencephaly (brain malformations), muscular dystrophy, and structural eye abnormalities (43, 44). Infants diagnosed with WWS rarely live past 12 months of age. Consistent with the severity of the disease, POMT1 and POMT2 knockout mice result in embryonic lethality (45).

POMGnT1

Human protein O-linked mannose β -1,2 N-acetylglucosaminyltransferase, also known by its acronym POMGnT1 (OMIM 606822), is a type II transmembrane glycosyltransferase that is found in the Golgi apparatus (46). POMGnT1 is expressed in a variety of mammalian tissue types, most prominently in skeletal muscle, brain tissue, and the eyes (43, 47). After POMT1 adds the O-mannose structure, POMGnT1 catalyzes the extension of the reducing-end mannose with the addition of a β -1,2 N-acetylglucosamine (GlcNAc) (44, 47). Additionally, this enzyme is essential for building the classical and the β -1,2/ β -1,6 branched structures primarily only observed in neural tissue (48, 49). The genotype-phenotype correlations of POMGnT1 mutants are arguably as diverse and complicated as those of POMT1, if not more so. The disease most often associated with mutation of the POMGnT1 gene is muscle-eye-brain disease (MEB; OMIM 253280). The clinical phenotype of MEB largely mirrors that of WWS; however, the phenotype of MEB is not as severe as WWS. The three major characterizing features of MEB are congenital muscular dystrophy, ocular abnormalities, and type II lissencephaly (43, 47). Although these features are very similar to those of

WWS, the life expectancy of a child born with MEB is 6-12 years, and in some cases even as high as 16 years; this is significantly longer than WWS patients (46, 47). Consistent with these observations, the POMGnT1 knockout mouse while severely afflicted is viable (50, 51).

Fukutin

Fukuyama congenital muscular dystrophy (FCMD; OMIM 253800) is largely caused by mutations in the fukutin gene, which codes for the putative glycosyltransferase fukutin (OMIM 607440) (6, 52). FCMD is very prevalent in Japanese populations, with a carrier frequency of 1 in 88 (53). Mutations in the fukutin gene have also been detected in patients showing a wide range of variability in dystroglycanopathy disease phenotypes; also including WWS, MEB, and a variety of limb-girdle muscular dystrophies (53). Although mutations in the fukutin gene have been correlated with severe dystroglycanopathies, the exact biochemical function of fukutin is not yet known (43). Mutations in fukutin have been shown to result in a hypoglycosylated non-functional α -DG (6). Of particular interest, fukutin does not clearly map to any CAZy-family of glycosyltransferases and may in fact be a post-glycosylational modification given its similarity to the LicD-proteins involved in phosphorylcholine transfer to sugars (54).

FKRP

Fukutin-related protein (FKRP; OMIM 606596), a homolog of fukutin, is another putative glycosyltransferase that does not fit into any defined CAZy-family but that has deleterious effects on α -DG glycosylation and function when mutated (55). Mutations in FKRP have been correlated with clinical presentation of MDC1C (OMIM 606612) and of limb-girdle muscular dystrophy 2I (LGMD2I; OMIM 607155) (6, 56, 57). Like that of its homolog fukutin, the exact biochemical function of FKRP is not well characterized and may relate to the presence of LicD-domains (54).

LARGE

LARGE is a Golgi-resident putative glycosyltransferase translated from a 650 kb gene. LARGE has two catalytic domains, based on sequence similarity to known glycosyltransferases, containing the classic Aspartic acid-X-Aspartic Acid (DXD, where X is any amino acid). One domain exhibits similarity to β -1,3-N-acetylglucosaminyltransferase, and the other shows similarity to *E. coli* protein WaaJ, a putative α -glycosyltransferase (58). Both catalytic sites are necessary for the proper functional glycosylation of α -DG (59). LARGE knockouts have been shown to have severe effects on functional glycosylation of α -DG (58). Also, removal of the LARGE-dependent modification on α -DG, requisite for laminin binding, has been shown to greatly alter the apparent molecular weight of α -DG (17). Conversely, over-expression of LARGE has been shown to inhibit cancer metastasis and rescue proper extracellular binding affinities of α -DG in mouse models with defective mutations in some of the other glycosyltransferases in the α -DG glycosylation pathway (59, 60). Over-expression of LARGE exhibits this same rescue function in cells derived from WWS, MEB, and FCMD patients; for this reason, modulation of LARGE expression and/or activity holds promise as a potential future therapeutic (27, 58). In the recently published study by Inamori (28), the group performed compositional sugar analysis in order to identify the composition of the LARGE dependent modification. The group found that the modification contains xylose (Xyl) and glucuronic acid (GlcA). This was confirmed by analysis of α -DG in a cell line lacking uridine 5'-diphosphate-xylose (UDP-Xyl), which showed that α -DG was not functionally glycosylated and therefore could not bind laminin even with over-expression of LARGE (28, 61). Using this information along with enzymatic and mutational studies, the group determined that LARGE is a

bifunctional glycosyltransferase with two separate catalytic domains and synthesizes a polysaccharide with repeating units of [-3Xyl- α 1,3GlcAb1-] (28). The exact placement of this repeating disaccharide on O-Man structures is unclear and other studies have illustrated that the LARGE-dependent modification can occur on mucin O-GalNAc-initiated structures and N-linked glycans in addition to O-Man structures (59, 60)

The mouse Large gene, an ortholog for human LARGE, is functionally null in the Large^{myd} mouse. In the Large^{myd} mouse, the causative deletion in the Large gene spans over 100 kb out of 650 kb. It is important to note, as a brief aside, that most animals have a LARGE ortholog, but *Drosophila* is a notable exception (62). The Large^{myd} mouse shows a vastly reduced lifespan and inhibited reproductive fitness along with muscle wasting (58). Large^{myd} mice show a loss of immunoreactivity with VIA4_I and IIH6, two monoclonal antibodies that recognize functionally glycosylated α -DG (63). It should also be noted that mammals have a Large2 gene that has yet to be fully characterized (24, 62, 64).

ISPD

The most recent addition to the list of causative genes for dystroglycanopathies, ISPD, was identified by two groups (38, 39). One group identified WWS causative mutations in the ISPD gene through cell fusion complementation assays using fibroblasts from WWS wildtype (38). The second group genotyped a cohort of patients and identified ISPD through genetic screening (39). Little is known about the function of this gene product. The bacterial homolog IspD is a member of the large glycosyltransferase family and functions as a nucleotide transferase and the WWS phenotype has been recapitulated in zebrafish through the knockdown of ispd (39). Identification of this gene introduces yet another gene product with unknown function that has been shown to be necessary for the production of a fully functional DGC and will certainly be an area of interest for new research in the dystroglycanopathy field.

Alpha-Dystroglycan and Other Diseases

Arenaviral Infection

As discussed, alpha-dystroglycan serves as a cell surface receptor for a number of components in the extracellular matrix, but the glycoprotein also serves as the receptor for certain arenaviruses (9-11). The Arenaviridae family is a zoonotic family of viruses with rodents serving as the natural host. The family consists of 22 virus species, while only 6 species have been shown to cause human disease. The family has been divided into two subgroups, Old World arenaviruses and New World, based on geological and phylogenetic evidence. The New World subset is further divided into 3 clades; A, B, and C. While Guanarito (GTOV), Junin (JUNV), Machupo (MACV), and Sabia (SABV) viruses, members of the New World clade B have been identified as the causative agent of Venezuelan, Argentine, Bolivian, and Brazilian hemorrhagic fevers respectively. However, the most common human infections are caused by the Old World arenaviruses, lymphocytic choriomeningitis virus (LCMV) and Lassa fever virus (LASV). LCMV is the less pathogenic of the two, often resulting in mild or asymptomatic infections. LASV, however, is highly pathogenic; infections are characterized by fever, pulmonary edema, encephalitis, respiratory distress, and mucosal bleeding. LASV infections mainly occur in West Africa and the rate of infections is estimated between 100,000 to 300,000 per year with a mortality rate of 5,000 per year.

Both LASV and LCMV as well as the remaining two Old World Arenaviruses, Mobala and Mopei, which do not cause human disease, were shown in 1998 by Cao to utilize α -DG as the cellular receptor required for subsequent endocytosis (9, 65). Binding affinities between

virus and receptor were analyzed in studies by Smelt *et al.* and showed that the higher binding affinity to α -DG seen with LCMV and LASV was directly related to the viral tropism, the ability to infiltrate the white pulp of the spleen, and subsequently the ability of the virus to establish a persistent infection (66). During the 2002 study by Spiropoulou *et al.*, viral species in clade C, but not A or B, of New World arenaviruses were also shown to utilize α -DG as the major cellular receptor (10). After receptor binding, the viruses have been shown to enter the cell via cholesterol dependent endocytosis rather than through the classical viral entry pathway involving direct fusion of virions with the cell membrane (65, 67-69). Characterization of the virus-receptor interaction identified the same LARGE-dependent mannose-initiated modification, likely at Thr-317/319, that mediates the interaction between α -DG and ECM ligands, as critical for function of α -DG as the cellular receptor for these viruses and demonstrated that arenavirus binding can be blocked by the addition of the mAb IIH6 (11, 70). Therefore the arenaviruses appear to be in competition with ECM ligands for the glycan-mediated receptor binding, a characteristic that could offer an explanation for the prevalence of mutations causing disruptions of this glycosylation pathway in certain populations, such as mutations in fukutin and FKR1P in Japan (71). Understanding the complete structure of the laminin-binding moiety, could lead to advancements in therapies to combat arenavirus infection.

Cancer and Metastasis

The development of human tumors is marked by the acquisition of a number of capabilities, including the activation of invasion and metastasis (72). In order for carcinomic cells to metastasize, they must first be liberated from the basement membrane (73). It is well established that interactions between cell surface proteins such as integrins and the DGC with ECM ligands, such as laminin, perlecan, and neurexin, are essential for the maintenance of cell-cell and cell-basement membrane connections (2, 13). Early studies of this initial step in metastasis revealed that an imbalance in proteolytic enzymes occurs at this stage, resulting in regulated degradation of ECM proteins (74, 75). Initially the focus was on members of the integrin family of ECM proteins, with multiple studies observing altered levels of expression in a number of different integrins in carcinoma cell lines, demonstrating that manipulations in expression levels may contribute to the proliferation or metastasis of tumor cells (75-77). In addition to the changes seen in expression levels of integrins in normal vs. tumor cells. Timmer *et al.* also observed disruption of the normal composition of the ECM (78).

In 2000, Losasso *et al.* recognized DG as a key component of the BM-Cell interaction that could also contribute to the disruption seen during tumorigenesis, noting aberrant processing of DG resulting in the truncation of β -DG and the loss of fully glycosylated α -DG, shown by reduction in laminin or antibody reactivity in a number of metastatic cell lines including breast, colon, and cervical carcinoma cell lines (7, 79). Integrating this information, with earlier studies demonstrating that α/β -DG associates with Grb2, a growth factor-associated adaptor protein, Losasso *et al.* hypothesized that these alterations seen with α - and β -DG in carcinoma cell lines could in turn have an effect on the signal transduction pathways resulting in metabolism and growth rate alterations in tumorigenic cells (7, 80, 81). Later studies have shown that α -DG is in fact correctly expressed and trafficked to the cell surface, but due to the silencing of LARGE, the receptor loses laminin reactivity (82). This claim is further supported with *in vitro* studies, by de Bernabé *et al.*, who reported rescued α -DG laminin binding in conjunction with a non-tumorigenic phenotype marked by enhanced cell adhesion and reduced cell migration, as a result of LARGE overexpression in epithelial-derived cancer cell lines (82). This data supports a model of altered expression of integrins, degradation of ECM proteins, and silencing of LARGE all contributing to the development of a metastatic phenotype in human epithelial cell lines.

Conclusion

The important role that O-mannosylation plays in human disease is becoming increasingly apparent. While most studies have been focused on O-mannosylation of α -DG, several studies have provided evidence that O-mannose initiated modifications occur on a number of other proteins (48, 83). Given that disruption of the DGC complex via defects in dystrophin does not show the severe lissencephaly phenotype and that dystroglycan knockout does not fully recapitulate the POMT1/2 knockout, it is likely that the O-mannosylation pathway is functionally modifying other proteins.

While the roles of a number of glycosyltransferases in the α -DG O-mannosylation pathway have been determined, several of the enzymes in this pathway have yet to be fully elucidated. Mutations in these enzymes are found within a number of types of dystroglycanopathies and direct genotype and phenotype correlations, for the most part, have yet to be established. Also, a complete structural elucidation of the functional O-mannose initiated glycans, that has yet to be realized, will likely reveal more enzymatic activities that will need to be assigned to putative disease-causing gene products. Aberrations in this glycosylation pathway are also linked to the development of metastatic phenotypes, but the necessity and sufficiency of O-mannosylation for the metastasis of tumor cells remains to be determined. The LARGE dependent modification on α -DG, has also been shown to be necessary for human infection by a number of members of the arenavirus family, although exploitation of this for therapeutics has yet to be achieved. A more complete understanding of the protein substrates, functional glycan structures, and enzymes of the O-mannosylation pathway will shed considerable light on the role of this pathway in dictating protein function and contributing to the pathophysiology of several diseases.

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Figure 1. The Dystrophin-Glycoprotein Complex

This multi-protein complex serves to anchor the extracellular matrix (ECM) to actin and other components of the cytoskeleton. O-mannosylated α -DG is a central component of this complex and serves as the binding partner for a number of extracellular matrix proteins (including laminin, perlecan, agrin and neurexin) and also as a receptor for certain members of the Arenaviridae family of viruses. The interaction between α -DG and its binding partners is glycan-mediated and disruption is linked to a number of congenital muscular dystrophies and has been implicated in tumor cell metastasis.

Figure 2. O-Mannose Glycan Structures

Classically, O-mannose is extended with GlcNAc in a $\beta 2$ -linkage. On α -DG this GlcNAc is typically seen further extended by galactose and sialic acid; the linkages and enzymes responsible for the additions are shown beside the glycans. However, the O-mannose of the laminin binding structure has been shown to be extended by GlcNAc in a novel $\beta 4$ -linkage and then further extended by GalNAc in a $\beta 3$ -linkage. The enzymes responsible for these additions have yet to be identified. The O-mannose of this structure is further modified by an unknown moiety, "X", in a phosphodiester linkage to the 6 position of the mannose; this "X" modification is essential for laminin binding. The complete identity of "X" has not been solved but recent studies have suggested that LARGE is responsible for the addition of the repeating disaccharide, [-3Xyl- $\alpha 1,3$ GlcA $\beta 1$ -] to this structure.

Table 1

Genetic mutations in glycosyltransferases and associated proteins that result in hypoglycosylation of α -DG and congenital muscular dystrophies. WWS=Walker-Warburg Syndrome, LGMD = Limb Girdle Muscular Dystrophy, MEB = Muscle Eye Brain Disease and MD = Muscular Dystrophy.

Gene	Protein	Disease
POMT1	Protein-O-mannosyltransferase 1	WWS LGMD2K
POMT2	Protein-O-mannosyltransferase 2	WWS LGMD2N
POMGnT1	O-Linked mannose β 1,2-N-acetylglucosaminyl-transferase	MEB LGMD
LARGE	Large	WWS MDC1D
FKTN	Fukutin	WWS, MEB-Like, FCMD, LGMD2M
FKRP	Fukutin-related protein	WWS, MEB-Like MDC1C, LGMD2I
ISPD	Ispd (<i>isoprenoid synthase domain-containing</i>)	WWS