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Finding the sweet spot: Assembly and Glycosylation of the Dystrophin-Associated Glycoprotein Complex

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Abstract

The dystrophin-associated glycoprotein complex (DGC) is a collection of glycoproteins that are essential for the normal function of striated muscle and many other tissues. Recent genetic studies have implicated the components of this complex in over a dozen forms of muscular dystrophy. Furthermore, disruption of the DGC has been implicated in many forms of acquired disease. This review aims to summarize the current state of knowledge regarding the processing and assembly of dystrophin associated proteins with a focus primarily on the dystroglycan heterodimer and the sarcoglycan complex. These proteins form the transmembrane portion of the DGC and undergo a complex multi-step processing with proteolytic cleavage, differential assembly, and both N- and O-glycosylation. The enzymes responsible for this processing and a model describing the sequence and subcellular localization of these events are discussed.

Introduction

Dystrophin and its associated proteins are critical for the normal function of both skeletal and cardiac muscle, as is evident from the severity of the disease resulting from their absence (Bushby et al., 2010a, 2010b; Norwood et al., 2007). The most common of these diseases is Duchenne muscular dystrophy (DMD), which was first described in the 19th century (Clarke and Gowers, 1874; Duchenne, 1867; Ross, 1883). Our understanding of this disease process was greatly enhanced with the identification of dystrophin as the protein whose loss resulted in DMD (E P Hoffman et al., 1987a). This discovery facilitated the characterization of an entire complex of proteins, collectively called dystrophin-associated glycoprotein complex (DGC; Figure 1). These proteins interact with dystrophin to mediate cellular interactions with the extracellular matrix important in membrane stabilization, force transmission, and synapse formation (Ervasti and Campbell, 1993, 1991; Ervasti et al., 1990; Yoshida and Ozawa, 1990). Mutations within many of these genes or in genes involved in post-translational modifications of DGC proteins have been demonstrated to cause multiple forms of recessive muscular dystrophy (Table 1).

Along with these genetic diseases, it has become evident that dystrophin and its related proteins are important in the pathophysiology of many acquired diseases. Patients with genetic disruptions of dystrophin clearly demonstrate that the loss of dystrophin is sufficient

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to cause significant cardiac disease. The marked reduction of dystrophin in patients with heart failure (Vatta et al., 2004, 2002) and viral myocarditis (Lee et al., 2000; Lim et al., 2013; Xiong et al., 2002) implicate dystrophin in the pathophysiology of these common forms of heart disease. The loss of dystrophin in the heart has been seen with pulmonary hypertension (Daicho et al., 2009) and in aging (Townsend et al., 2011). Reductions in dystrophin and the DGC have also been implicated in cancer cachexia (Acharyya et al., 2005) and disuse atrophy (Chockalingam et al., 2002). Given the importance of the DGC to the pathogenesis of many diseases, this review will focus on recent developments in our understanding of the assembly and function of these proteins.

DGC Components

Dystroglycan

Dystroglycan (DG) is a heterodimer that consists of a transmembrane β-subunit and a large, heavily glycosylated α-subunit (Figure 1). These proteins were first identified as part of the complex that tightly associates with dystrophin (Ervasti et al., 1990). The α-and β-subunits of DG are proteolytic cleavage products of a single polypeptide (Ibraghimov-Beskrovnaya et al., 1992). The C-terminal domain of β-DG faces the cytosol, where it interacts with dystrophin or utrophin (Jung et al., 1995; Matsumura et al., 1992a). This interaction is thought to localize DG and associated proteins to a defined subcellular region. On the extracellular surface α-DG, anchored to β-DG, functions as a receptor for extracellular matrix components such as laminin, neurexin, and agrin (Ervasti and Campbell, 1993; Michele et al., 2002). DG is expressed widely throughout the body, with the highest levels present in striated muscle and the brain (Ibraghimov-Beskrovnaya et al., 1993). The main function of DG is centered on its ability to bind to various elements of the extracellular matrix, a process that is critically dependent on post-translational glycosylation (Michele et al., 2002).

Dystroglycan Processing

The dystroglycan gene (DAG1) expression is regulated by a combination of chromatin remodeling and transcription factors binding to SP1 and E-Box sites in the promoter region (Rettino et al., 2009). This promoter is relatively active in myoblasts and displays increased activity during differentiation (Noguchi et al., 1999). Following the excision of two large introns the mature mRNA is translated and the protein is inserted into the ER membrane (Ibraghimov-Beskrovnaya et al., 1993, 1992). Dystroglycan is cleaved into a large extracellular domain (α-DG) and a smaller transmembrane protein (β-DG). While both α- and β-DG are glycoproteins, the glycosylation of α-DG is a particularly complex process involving many glycosyltransferases and demonstrating distinct tissue (Ervasti et al., 1997) and developmental regulation (Goddeeris et al., 2013; Leschziner et al., 2000). A tremendous amount of work has been done to understand the processing of DG. Over half a dozen genetic diseases have been linked to alterations in this pathway. The following section will focus on describing a model of DG glycosylation that attempts to incorporate findings ranging from patients to cell lines.

The cleavage of dystroglycan into two polypeptides is critical for proper post-translational processing (Esapa et al., 2003; Jayasinha et al., 2003). Both α- and β-DG are N-glycosylated; although these modifications are limited in size and number (Ervasti and Campbell, 1991; Ibraghimov-Beskrovnaya et al., 1992), they are critically important for subsequent processing (Esapa et al., 2003). α-DG has two globular domains flanking a central mucin domain that is characterized by a high concentration of serine, threonine, and proline residues and is heavily glycosylated (Ibraghimov-Beskrovnaya et al., 1992). In addition to proteolysis and N-glycosylation, nearly half of the O-glycosylation of α-DG begins with the addition of mannose (Stalnaker et al., 2010). Mannose-1-phosphate is converted to GDP-mannose by guanosine diphosphate mannose pyrophosphorylase B (GMPPB; Carss et al., 2013). GDP-mannose serves as a substrate for dolichol-phosphate-mannose (Dol-P-Man) synthase, an enzyme consisting of three subunits, DPM1-3 (Lefeber et al., 2009). Dol-P-Man is the substrate utilized by a variety of mannosyltransferases, including those involved in the glycosylation of α-DG. The function of the enzyme isoprenoid synthase domain (ISPD) has not been clearly defined, however, its homologous enzymes in plants and bacteria suggest it may have a role in synthesizing a new nucleotide sugar (Roscioli et al., 2012; Willer et al., 2012). The protein *O*-mannosyltransferase (POMT)-1 and POMT-2 transfer mannose to the α-DG polypeptide (Beltran-Valero de Bernabe et al., 2002; Manya et al., 2004; Willer et al., 2002). A subset of these mannose moieties are modified by POMGnT2, which adds an *N*-Acetyl glucosamine in a β1-4 configuration to the mannose, followed by the addition of an *N*-acetyl glacatosamine by B3GALnT2 (Yoshida-Moriguchi et al., 2013). The kinase SGK196 is responsible for the phosphorylation the sixth carbon of mannose in this trisaccharide (Yoshida-Moriguchi et al., 2013). Failure of any of these processes completely prevents the subsequent ability of α-DG to bind its extracellular matrix ligands (Beltran-Valero de Bernabe et al., 2002; van Reeuwijk et al., 2005). The addition of *O*-linked mannose has been documented throughout the mucin domain, but it is concentrated in the N-terminal half of this domain (Kanagawa et al., 2004; Stalnaker et al., 2010). As DG leaves the ER and transits to the Golgi, it has been cleaved into two subunits, N-glycosylation has been initiated, and *O*-linked Mannose moieties have been attached and partially modified (Figure 2).

Within the Golgi, DG interacts with many glycosyltransferases and other regulatory proteins. Protein *O*-mannose beta-1,2-*N*-acetylglucosaminyltransferase (POMGnT1) is present within the Golgi and attaches an *N*-acetylglucosamine to the *O*-linked mannose moieties (Yoshida et al., 2001). Also in the Golgi, POMGnT1 forms a complex with fukutin, a protein whose disruption causes Fukuyama-type congenital muscular dystrophy (Kobayashi et al., 1998; Xiong et al., 2006). The function of fukutin is currently unknown; but interestingly, it shares homology with a yeast protein that regulates mannose phosphorylation (Aravind and Koonin, 1999). Furthermore, phosphorylated mannose is a poor substrate for POMGnT1 and thus prevents the addition of *N*-acetylglucosamine (Mo et al., 2011). These data raise the interesting hypothesis that a complex containing POMGnT1, fukutin, and α-DG is responsible for preparing α-DG to be a suitable substrate for subsequent steps. Nearly all of the mannose moieties are expanded in the Golgi through the addition of *N*-acetylglucosamine by POMGnT1 (Yoshida et al., 2001; Zhang et al., 2002). Most of these receive an additional galactose and a bit more than half of these receive a

terminal sialic acid moiety (Stalnaker et al., 2010). This later motif has been extensively characterized in isolated mature α-DG (Chiba et al., 1997; Sasaki et al., 1998).

The ability to bind laminin is an essential function of DG and is completely dependent on the presence of a unique glycan (Michele et al., 2002). This glycan is added by a glycosyltranserase called LARGE (Like-acetylglucoseaminyltransferase). The LARGE-glycan consists of a long polymer of 3-xylose-α-1,3-glucuronic acid (Inamori et al., 2012) that is attached to the α-DG backbone at a phosphorylated mannose group (Yoshida-Moriguchi et al., 2010). Most of the evidence supports a model whereby the LARGE-glycan is added to only the *O*-linked mannose group attached to Thr379 of α-DG (Kanagawa et al., 2004; Stalnaker et al., 2011b; Yoshida-Moriguchi et al., 2010), although other sites may also contribute. Increased expression of LARGE results in increased LARGE-glycan deposition (Gumerson et al., 2013; Yu et al., 2013; Zhang and Hu, 2012). However, with overexpression there is nonspecific addition of LARGE-glycan to non-DG proteins (Zhang and Hu, 2012).

Fukutin-related protein (FKRP) is a homodimer that also colocalizes with fukutin in the Golgi (Esapa et al., 2002). Mutations within FKRP result in muscular dystrophy-dystroglycanopathy type 5, a combined clinical descriptor encompassing both congenital muscular dystrophy type 1 (MDC1C) and the milder limb-girdle muscular dystrophy 2I (LGMD2I; Table 1; Alhamidi et al., 2011; Brockington et al., 2001a, 2001b). The effect of these mutations on α-DG glycosylation is variable with some patients displaying very little LARGE-glycan, while others have only slight reductions (Brockington et al., 2001a, 2001b). Similarly, mouse models of FKRP mutations also have variable phenotypes ranging from no LARGE-glycan to nearly normal levels (Blaeser et al., 2013). In samples from patients with FKRP mutations there is an increased gel mobility of the LARGE-glycan immunoreactivity (Blaeser et al., 2013; Brockington et al., 2001a). The gel migration of the α-DG core protein in FKRP mutant mice is not altered by aqueous hydrofluoric acid treatment, which cleaves phosphodiester bonds and releases the LARGE-glycan. Therefore, the lack of an effect indicates that there is less LARGE-glycan and suggests that FKRP may function to increase the efficiency of LARGE-glycan addition (Kuga et al., 2012). Interestingly, despite this proposed role in the maturation of α-DG, FKRP accompanies the entire DGC to the surface membrane (Beedle et al., 2007). Other studies demonstrate that the N-terminal domain of α-DG is essential for the addition of the LARGE-glycan, but is cleaved off by a furin convertase prior to final transport to the surface membrane (Kanagawa et al., 2004).

As noted above, the LARGE-glycan accounts for only a very small portion of the significant level of *O*-glycans present on α-DG. The remainder of these moieties are either the POMGnT1-dependent mannose-initiated or *O*-linked *N*-acetylgalactosamine initiated mucin groups (Stalnaker et al., 2011a, 2010). The latter of these glycans is initiated in the Golgi by the actions of polypeptide *N*-acetylgalactosaminyltransferase (Homa et al., 1993; Mo et al., 2011; Röttger et al., 1998; White et al., 1995). Like the mannosylation in the ER, *N*-acetylgalactosaminylation occurs stochastically on specific Ser/Thr residues throughout the central mucin domain of α-DG, although they appear to occur more frequently in the C-terminal half of the domain (Stalnaker et al., 2010). The importance of these tetrasaccharides and trisaccharides for LARGE function is evident by the dramatic decrease in LARGE-

glycan addition in patients with mutations in POMGnT1 or the inhibition of ppGalNAcT, the enzymes that initiate these glycans (Esapa et al., 2003; Michele et al., 2002). The mechanism by which these changes limit addition of the LARGE-glycan are not clear, but likely result from the significant structural differences imparted by O-glycosylation on α-DG.

The majority of these *O*-glycans terminate with a sialic acid moiety (Stalnaker et al., 2010). Despite its abundance, removal of the terminal sialic acid has no significant effect on α-DG laminin binding activity, although it does prevent the binding of several lectins (Combs and Ervasti, 2005). Other studies demonstrate that overexpression of LARGE in cells with defective sialic acid metabolism results in normal levels of LARGE-glycan addition (Patnaik and Stanley, 2005). However patients with disruption of sialic acid synthesis display a variable phenotype; most appear to retain the LARGE-glycan and laminin binding (Broccolini et al., 2005; Saito et al., 2004), although some patients display a loss of the LARGE-glycan (Huizing et al., 2004).

There are clear differences in the glycosylation of DG in different tissues (Ervasti et al., 1997), but the underlying mechanism remains unclear. Recent studies in mice lacking LARGE indicate that tissue-dependent differences in the gel migration of the α-DG core protein remain (Goddeeris et al., 2013), suggesting that *O*-glycans, other than LARGE-glycan, contribute to these differences. Consistent with this model is the increased gel migration of the α-DG protein core with the loss of POMGnT1 function, which transfers *N*-acetylglucosamine to mannose (Willer et al., 2012). Differences in tissue expression of other α-DG processing enzymes have also been described and may contribute to these tissue-specific forms of α-DG (Homa et al., 1993; Margeta et al., 2009; White et al., 1995).

The importance of the LARGE-glycan for the binding of extracellular matrix proteins is well established (Barresi et al., 2004; Michele et al., 2002). The function of the other glycosylation sites remains less clear. One possible function is that these modifications improve the interaction between α- and β-DG (Zhang and Hu, 2012) or perhaps to protect β-DG from the action of extracellular proteases (Hnia et al., 2006). Another intriguing possibility is that these additional *O*-glycan structures provide mechanical support of the LARGE-glycan domain. Full O-glycosylation of the mucin domain would be expected to greatly increase the stiffness of the region (Jentoft, 1990). This stiffness may be important for extending the LARGE-glycan containing N-terminus of α-DG out toward the extracellular matrix components it interacts with.

Sarcoglycan Complex

The sarcoglycan complex (SGC) is a group of four tightly associated proteins that have been implicated in causing several forms of recessive limb-girdle muscular dystrophies (LGMD). This section will introduce each of the sarcoglycans (SG) and then will discuss what is known regarding the assembly of this complex.

α-Sarcoglycan—α-Sarcoglycan was the first member of the SGC to be identified as the gene responsible for causing LGMD2D (Matsumura et al., 1992b). The gene encoding α-SG is located on human chromosome 17 and consists of 10 exons (Roberds et al., 1994). The

protein has two putative N-glycosylation sites and a single transmembrane domain with a relatively short intracellular C-terminal domain (Roberds et al., 1993). Most disease causing mutations are found in the extracellular domain (Bonnemann et al., 1995; McNally et al., 1994; Piccolo et al., 1995). α-SG contains a divalent cation dependent ecto-ATPase activity within its extracelluar domain that has been demonstrated in both myoblasts and HEK-293 cells (Betto et al., 1999; Sandona et al., 2004). The physiological importance of this activity is currently unknown.

ε-Sarcoglycan—Muscular dystrophy resulting from mutations in α-SG have milder cardiac disease than mutations caused by other members of the SGC (Carrie et al., 1997). This is explained, in part, by the presence of ε-SG, an α-SG homologue (Ettinger et al., 1997; McNally et al., 1998). ε-SG is widely expressed in non-skeletal muscle tissues, including the heart (Ettinger et al., 1997; Imamura et al., 2005; McNally et al., 1998; Straub et al., 1999). The ε-SG gene structure is similar to that of α-SG (McNally et al., 1998) and in the absence of α-SG, ε-SG can support the SGC (Liu and Engvall, 1999). ε-SG is expressed early in development in striated muscle and is found in smooth muscle tissues in adults (Imamura et al., 2005; Straub et al., 1999). ε-SG levels decrease in skeletal muscle shortly after birth (Liu and Engvall, 1999; Straub et al., 1999). Ablation of both α- and ε-SG results in the loss of the cardiac SGC and a phenotype much more severe than that present in either knockout individually (Lancioni et al., 2011).

β-Sarcoglycan—β-SG is a 43 kDa protein, the mutation of which has been linked to LGMD2E (Bonnemann et al., 1995; Lim et al., 1995). The β-SG gene is found on chromosome 4 and consists of 6 exons (Bonnemann et al., 1995; Duclos et al., 1998; Lim et al., 1995). The protein contains a single transmembrane domain and a short intracellular N-terminal domain. The longer extracellular domain contains three N-glycosylation sites and is the location of most of the disease causing mutations (Bonnemann et al., 1998; Lim et al., 1995). Loss of β-SG results in the complete absence of the SGC without significant changes in transcript levels (Araishi et al., 1999). Importantly, laminin, dystrophin, and β-DG are normally localized (Araishi et al., 1999; Duclos et al., 1998); although expression of fully glycosylated α-DG appears to be reduced (Araishi et al., 1999).

γ-Sarcoglycan—γ-SG is a 35 kDa protein also with a single transmembrane domain and an extracellular C-terminal domain, which contains a single N-glycosylation domain and a series of conserved cysteines (McNally et al., 1996; Noguchi et al., 1995). Mutations in γ-SG cause LGMD2C, with most of the mutations occurring in the extracellular domain (McNally et al., 1996; Torelli et al., 2005). Loss of γ-SG results in the absence of the other three SGC components (Hack et al., 1998; McNally et al., 1996) σ-Sarcoglycan σ-SG is also a 35 kDa protein that shares significant homology with γ-SG. Like γ-SG, σ-SG consists of a single transmembrane domain with a small intracellular N-terminus and a larger extracellular C-terminal domain, with a single N-glycosylation site and the cluster of cysteine residues present in several other members of the SGC (Nigro et al., 1996b). Mutations in σ-SG result in LGMD2F (Nigro et al., 1996a; Passos-Bueno et al., 1996) and the loss of the entire SGC (Hack et al., 2000; Straub et al., 1998). Interestingly, similar to the

absence of β-SG, the loss of σ-SG results in the disproportional loss of the LARGE-glycan expression relative to β-DG (Sakamoto et al., 1997; Straub et al., 1998).

ζ-Sarcoglycan—ζ-SG is homologous to gamma- and delta-SG with 55-57% amino acid identity and 74-75% similarity. It is present in the SGC in both skeletal and cardiac muscle, especially in the absence of γ- or σ-SG (Wheeler et al., 2002). ζ-SG also contains the conserved cluster of cysteine residues that are found in β-,γ-, and σ-SG.

Sarcospan—Sarcospan (SSPN) is a 25kDa protein with 4 transmembrane domains with both N- and C-termini on the intracellular face that is localized to cardiac and skeletal muscle sarcolemma. Primary expression is in striated muscle, although lower levels of expression are present in the lung, brain, and testes. SSPN is markedly down-regulated in DMD patients and in dystrophin deficient mdx mice, including the heart where the DGC is largely intact, suggesting a unique dependence on dystrophin for stabilization (Crosbie et al., 1999, 1997). SSPN is also expressed at the neuromuscular junction, where it is stabilized by either dystrophin or utrophin (Crosbie et al., 1999). SSPN expression is also dependent on the presence of an intact SGC (Araishi et al., 1999; Coral-Vazquez et al., 1999; Crosbie et al., 2000, 1999). Loss of SSPN does not result in a significant myopathy, although molecular changes include a reduction in dystrophin binding to the DGC and increased susceptibility to lengthening contractions (Lebakken et al., 2000; Marshall et al., 2012a). While high levels of overexpression are detrimental, lower levels of human SSPN expression increase the presence of the DGC and utrophin in the sarcolemma of mdx skeletal muscle resulting in improved muscle function (Peter et al., 2008, 2007). SSPN is capable of forming higher order oligomers (Marshall and Watson, 2013; Miller et al., 2007), which in other structurally related proteins results in the formation of a lattice network. It has been proposed that SSPN functions, in part, to hold the components of the DGC in tight proximity (Marshall and Watson, 2013).

Assembly of the SGC—The individual components of the SGC are inserted into the membrane of the ER where the process of N-glycosylation begins. Blockade of ER export demonstrates that the initial addition of mannose and subsequent addition of sialic acid and *N*-acetylglucosamine all occur within the ER (Noguchi et al., 2000). The *N*-glycan structures on the SGs are critically important for subsequent trafficking to the membrane and association with the DG heterodimer (J. Chen et al., 2006; Noguchi et al., 2000; Shi et al., 2004). The timing and location of the interaction of SSPN with the reminder of the complex is not clear, although there is evidence that SSPN is present in the ER/Golgi compartment and that transgenic expression of SSPN alters the glycosylation of α-DG in the Golgi (Marshall et al., 2012b). Current evidence suggests that the SGC forms around a complex of β- and σ-SG (Chan et al., 1998; Noguchi et al., 2000) and is capable of binding to co-expressed β-DG/dystrophin complex (J. Chen et al., 2006). When expressed in HEK cells the β-/σ-SG dimer is sufficient to traffic to the membrane (Chan et al., 1998; J. Chen et al., 2006; Draviam et al., 2006a; Noguchi et al., 2000). The next significant complex is the β-/γ-/σ-SG trimer; each of these proteins contains a conserved cluster of cysteine residues that participate in intramolecular disulfide bond formation that is important for trafficking of the complex (Chan et al., 1998; J. Chen et al., 2006). The final form of the SGC is

completed with the addition of α-SG (Noguchi et al., 2000). α-SG, which binds to the γ-SG subunit, is capable of being transported to the plasma membrane independent of other parts of the SGC, however it is not stable at the cell surface without the rest of the complex (J. Chen et al., 2006; Draviam et al., 2006b; Noguchi et al., 2000; Shi et al., 2004). Many of the disease-causing mutations in the SGC affect either the stability of the proteins or involve mutations that disrupt the formation of these intermediate complexes (J. Chen et al., 2006; Draviam et al., 2006a; Holt and Campbell, 1998; Shi et al., 2004). The SGC is largely assembled and glycosylated within the ER and is tightly associated with the partially processed DG heterodimer as it transits to the Golgi (Noguchi et al., 2000). Furthermore, the addition of the LARGE-glycan, assessed by IIH6 immunoreactivity, to α-DG is critically dependent on the presence of an intact SGC (Hack et al., 2000; Straub et al., 1998). While the SGC will form without DG, it is unstable and continued expression is dependent on the presence of an intact DG (Cote et al., 2002; Holt and Campbell, 1998; Kanagawa et al., 2004; Michele et al., 2009)

Dystrophin and Utrophin

Dystrophin is the protein product of the DMD gene that is responsible for Duchenne muscular dystrophy (E P Hoffman et al., 1987a). The dystrophin protein consists of four major domains, an N-terminal actin binding domain, a central rod domain with 24 spectrin-like repeats, a cysteine-rich β-DG binding domain, and a carboxy-terminal domain (E P Hoffman et al., 1987a, 1987b; Koenig and Kunkel, 1990). Utrophin is a homologous protein with a similar domain structure (Matsumura et al., 1992a; Tinsley et al., 1992). Furthermore, overexpression of utrophin has been shown to largely rescue the phenotype of the mdx mouse (Tinsley et al., 1998) and utrophin expression correlates with a milder phenotype in DMD patients (Kleopa et al., 2006). Much has been written regarding the function of dystrophin and utrophin, but for the purposes of this review, only their ability to bind to the components of the DGC will be explored. The proteins of the DGC were first identified by their absence in skeletal muscle from patients with DMD (Ervasti et al., 1990; Ohlendieck and Campbell, 1991). In skeletal muscle, utrophin is normally localized to the neuromuscular junction where it binds to β-DG and the SGC to aid in the formation of the synaptic structure (Matsumura et al., 1992a; Tinsley et al., 1992). In cardiac tissue, utrophin also has a different subcellular localization pattern compared to dystrophin, suggesting it has a unique function in this tissue as well (Pons et al., 1994). In the absence of dystrophin, utrophin can largely replace dystrophin as evidenced by the severity of the dystrophy present in mice lacking both utrophin and dystrophin (Deconinck et al., 1997; Grady et al., 1997) and the ability of utrophin overexpression to significantly improve the phenotype of dystrophin-deficient mice (Rafael et al., 1998). In skeletal muscle, the absence of dystrophin results in dramatic decreases in the amount of DGC proteins that are present (Ervasti et al., 1990; Ohlendieck and Campbell, 1991). In smooth muscle, much of the DGC remains intact without dystrophin, but is absent in the dystrophin/utrophin double knockout (Straub et al., 1999), indicating that utrophin is largely able to compensate for the absence of dystrophin. Interestingly, the DGC is largely intact in the dystrophin-deficient myocardium with or without utrophin (Bies et al., 1997; Matsumura et al., 1992a; Sharpe et al., 2013; Townsend et al., 2007).

The roles of dystrophin and utrophin in the processing and stabilizing of the DGC are not clear. Both dystrophin and utrophin messages are expressed very early in muscle differentiation, but dystrophin protein does not accumulate until later in the differentiation process (Noguchi et al., 2000, 1999; Tanaka and Ozawa, 1990; Tomé et al., 1994). During early differentiation, utrophin is prominent at the surface of the myotube while dystrophin expression is largely cytoplasmic in nature as are both β-DG and the sarcoglycans (Noguchi et al., 2000). This data suggests that in developing skeletal muscle, dystrophin interacts with the DGC components prior to insertion into the surface membrane. This raises the possibility that dystrophin may modulate the processing of the DGC as it moves through the cellular export pathways. Less is known about the maturation of the DGC in cardiac tissues, but recent studies suggest that dystrophin and utrophin may have a role in the glycosylation of α-DG in this tissue (Sharpe et al., 2013). This study provides evidence that the addition/maturation of non-LARGE-glycan O-glycosylation is dependent on the presence of dystrophin or utrophin (Sharpe et al., 2013). It is not clear if these changes in glycosylation result from the pathology present in these mice or if they provide support for a model where dystrophin or utrophin directly affect the processing and assembly of the DGC in the Golgi. In skeletal muscle, the absence of dystrophin results in the accumulation of the DGC components in the ER/Golgi compartment (Marshall et al., 2012b). In both skeletal and cardiac muscle increases in dystrophin levels result in increased levels of the DGC (Cox et al., 1993; Townsend et al., 2007). This data suggests that dystrophin is the rate-limiting step in the accumulation of the DGC at the surface membrane; the more dystrophin binding sites, the more DGC is stabilized and saved from the proteasome (Bonuccelli et al., 2003). There is significant evidence indicating that the DGC is present in distinct domains within the surface membranes (Byers et al., 1991; Klietsch et al., 1993; Ohlendieck et al., 1991; Watkins et al., 1987), however, the functional importance of these distinct domains is not clear.

Other Peripheral Components of the DGC—In addition to the membrane-bound components of the DGC, several soluble proteins are found tightly associated with dystrophin and the rest of the DGC. The most abundant of these are syntrophin (Ahn et al., 1994; Ohlendieck and Campbell, 1991) and dystrobrevin (Dwyer and Froehner, 1995). In the DGC, syntrophin's PDZ domain facilitates the localization of a variety of binding partners ranging from nNOS (Brenman et al., 1995) and α_{1D}-adrenergic receptors (Z. Chen et al., 2006) to ion channels (Gavillet et al., 2006; Vandebrouck et al., 2007) and aquaporin (Adams et al., 2001). The function of dystrobrevin is less clear. Its structure suggests that it too functions to bind proteins together, but the targets of these interactions are largely cytoskeletal in nature (Albrecht and Froehner, 2004; Benson et al., 2001; Mizuno et al., 2001; Newey et al., 2001). Dystrobrevin's interaction with both dystrophin and the sarcoglycan complex also suggests a potential role reinforcing dystrophin binding to the membrane (Bunnell et al., 2008; Sadoulet-Puccio et al., 1997; Yoshida et al., 2000). Both syntrophin and dystrobrevin have multiple isoforms and splice variants that display unique subcellular localization and binding interactions, however, the importance of these individual isoforms is less clearly understood. In addition to syntrophin and dystrobrevin, there are a variety of other proteins that have been shown to interact with dystrophin and the DGC, including ankyrin-B and –G (Ayalon et al., 2008), microtubules (Prins et al., 2009),

cavin-1, CRYAB, and AHNAK1 (Johnson et al., 2012). Little is known regarding the timing and localization of the association of these soluble proteins with the DGC core proteins.

Conclusion

The DGC is essential to the normal functioning of striated muscle and many other tissues. We have significantly improved our understanding of the role these molecules play in muscle function. The data reviewed here indicate that the transmembrane core DGC proteins associate early within the protein export pathways (Figure 2; Noguchi et al., 2000). This tight association is essential for the normal processing and function of the mature DGC. The addition of dystrophin/utrophin appears to be required for these complexes to exit the Golgi, but the role of other components of the DGC remains unclear. Despite the detail by which this process has been defined many questions about the role of α-DG glycosylation remain, including: how does it define ligand selectivity, does it modify the structural features of the core protein, or dose it possess some other function? Recent studies have demonstrated that α-DG is present in significant excess relative to dystrophin, suggesting that most of this protein is not normally associated with dystrophin (Johnson et al., 2013); the function of such a complex remains unclear. Further complexity arises from the diversity of DGC structures within cells (surface vs. NMJ) and between different cell types (skeletal vs. cardiac muscle) and the functional significance of these differences will likely provide insight into role of the DGC in a variety of tissues. Diseases of the DGC are largely incurable in part because of a poor mechanistic understanding of the pathophysiology resulting from the loss of these proteins. A more complete understanding of the mechanism of disease would allow the identification of specific pathways that may be amenable to the development of specific therapeutics. Furthermore, there is increasing evidence that the proteins in the DGC may have a significant role in the pathophysiology of more common acquired diseases ranging from cancer cachexia to heart failure (Acharyya et al., 2005; Fearon et al., 2012; Lim et al., 2013; Toyo-Oka et al., 2004; Vatta et al., 2002). Further studies into the physiology of the DGC will be important for the development of new therapies for both rare genetic disorders and more common diseases where the DGC has been implicated.

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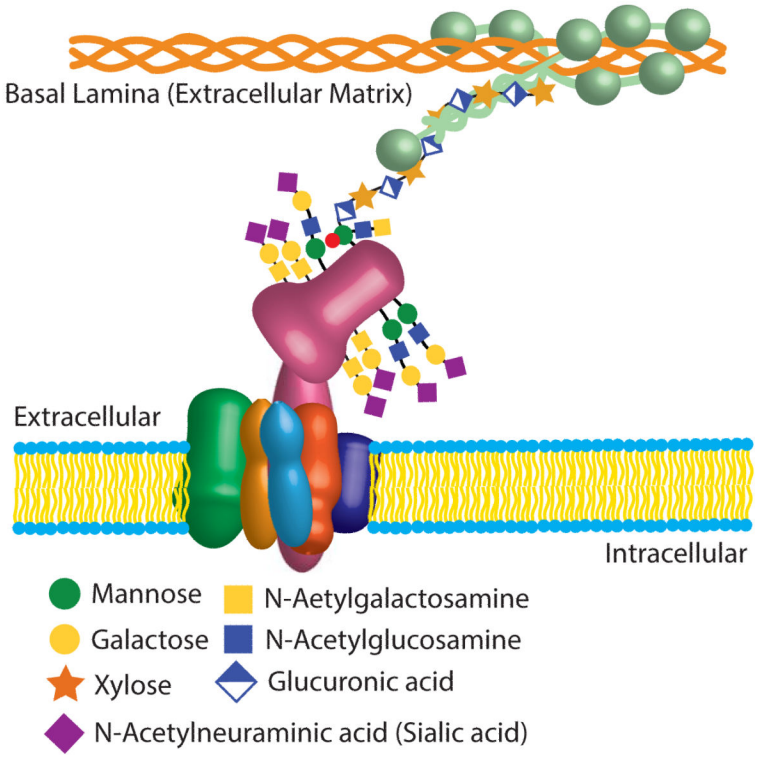

Figure 1.

A schematic cartoon of the DGC in the sarcolemmal membrane. The sarcoglycan complex (SGC) consists of α-SG (green), β-SG (orange), γ-SG (gold), σ-SG (light blue), and sarcospan (purple). This protein complex associates with β-dystroglycan (DG; pink) which binds to α-DG. α-DG is heavily glycosylated and functions as a receptor for laminin (light green), which in turn binds to collagen (orange). All of the components of the DGC shown here are also N-glycosylated; these features are not shown, but details can be found in the text.

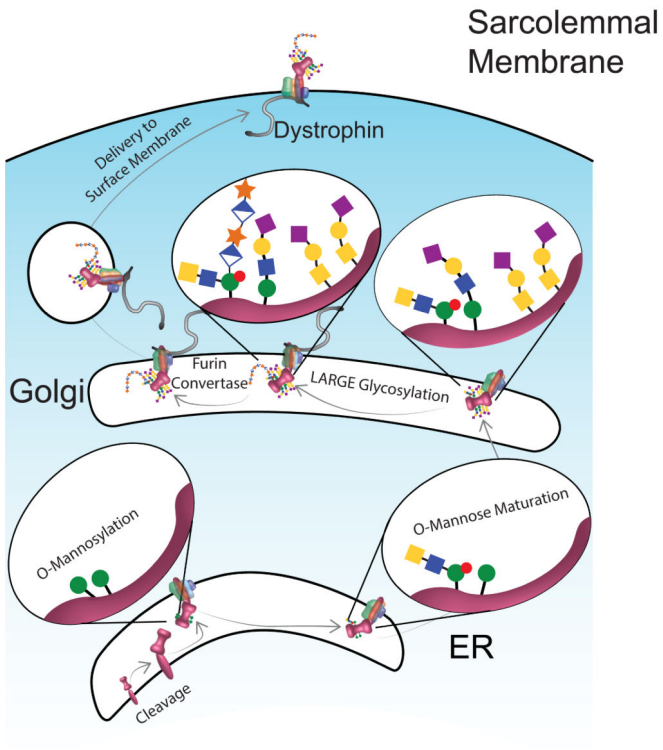

Figure 2.

A model of the processing of dystroglycan (DG; pink). The DAG polypeptide is cleaved into α- and β-DG. While shown in the ER, the nature of the protease and its precise subcellular location are unknown. *O*-linked mannosylation (green circles) of α-DG occurs within the ER. During O-mannose maturation, mannose moieties on which the LARGE-glycan will be added are phosphorylated (red circle) and *N*-acetylglucosamine (filled blue square) and *N*-acetylgalactosamine (filled yellow square) are added. Following transit to the Golgi, additional *O*-glycosylation occurs with many structures capped with galactose (yellow circle) and sialic acid (purple diamond). Next a polymer of glucuronic acid (half-filled diamond) and xylose (orange star) is added by the glycosyltransferase LARGE. Following the cleavage of the N-terminal globular domain of α-DG by a furin convertase the complex is exported to the sarcolemmal membrane. The number of sites and structures of the glycosylation moieties has been simplified for clarity (see text for more details). Note the subcellular location where dystrophin first interacts with the DGC is not clear, while evident at the membrane so data suggests that dystrophin has a role in exporting the DGC from the Golgi (see text for details).

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Table 1

Gene	OMIM ID	Disease	Reference
Dystrophin	300377	DMD, BMD, XLCM	(E. P Hoffman et al., 1987; Towbin et al., 1993)
γ-Sarcoglycan	608896	LGMD-2C	(Noguchi et al., 1995)
α-Sarcoglycan	600119	LGMD-2D	(Matsumura et al., 1992b)
β-Sarcoglycan	600900	LGMD-2E	(Bonnemann et al., 1995)
δ-Sarcoglycan	601411	LGMD-2C	(Nigro et al., 1996a)
Protein O-mannosyltransferase-1 (POMT-1)	607423	MDDG-A1; LGMD-2K	(Beltran-Valero de Bernabe et al., 2002)
Protein O-mannosyltransferase-2 (POMT-2)	607439	MDDG-A2; LGMD-2N	(Willer et al., 2002)
Protein O-mannose β-1,2-N-Acetylglucosaminyltransferase (POMGNT1)	606822	MDDG-A3; LGMD-2O	(Yoshida et al., 2001)
Fukutin	607440	MDDG-A4; LGMD-2M	(Kobayashi et al., 1998)
Fukutin-related protein (FKRP)	606596	MDDG-A5; LGMD-2I	(Brockington et al., 2001a)
Acetylglucosaminyltransferase-like protein (LARGE)	603590	MDDG-A6	(van Reeuwijk et al., 2007)
Isoprenoid synthase domain-containing protein (ISPD)	614631	MDDG-A7	(Roscioli et al., 2012; Willer et al., 2012)
Glycosyltransferase-like domain-containing protein 2 (GTDC2)	614828	MDDG-A8	(Manzini et al., 2012)
Dystrophin-associated glycoprotein 1 (DAG1); Dystroglycan	128239	MDDG-C9; LGMD-2P	(Hara et al., 2011)
Transmembrane protein 5 (TMEM5)	605862	MDDG-A10	(Jae et al., 2013)
β-1,3-N-Acetylgalactosaminyltransferase 2 (B3GALNT2)	610194	MDDG-A11	(Stevens et al., 2013)
Protein kinase-like protein (SGK196)	615247	MDDG-A12	(Jae et al., 2013)
b-1,3-N-Acetylglucosaminyltransferase 1	605517	MDDG-A13	(Buysse et al., 2013)
GDP-Mannose pyrophosphorylase B (GMPPB)	615320	MDDG-A14	(Carss et al., 2013)
Dolichyl-phosphate Mannosyltransferase 2 (DPM2)	603564	CDG1U	(Barone et al., 2012)
Dolichyl-phosphate Mannosyltransferase 3 (DPM3)	605951	CDG1O	(Lefeber et al., 2009)
Dolichol kinase (DOLK)	610746	CDG1M	(Lefeber et al., 2011)

*LGMD-Limb girdle muscular dystrophy; MDDG-Muscular dystrophy-dystroglycanopathy; CDG-Congenital disorder of glycosylation