CHAPTER FIVE

Biology of the Striated Muscle Dystrophin–Glycoprotein Complex

James M. Ervasti *and* Kevin J. Sonnemann

Contents

Abstract

Since its first description in 1990, the dystrophin–glycoprotein complex has emerged as a critical nexus for human muscular dystrophies arising from defects in a variety of distinct genes. Studies in mammals widely support a primary role for the dystrophin–glycoprotein complex in mechanical stabilization of the plasma membrane in striated muscle and provide hints for secondary functions in organizing molecules involved in cellular signaling. Studies in model organisms confirm the importance of the dystrophin–glycoprotein complex for muscle cell viability and have provided new leads toward a full understanding of its secondary roles in muscle biology.

Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, Minnesota 55455

International Review of Cytology, Volume 265
ISSN 0074-7696, DOI: 10.1016/S0074-7696(07)64005-4

Key Words: Dystrophin, Dystroglycan, Dystrobrevin, Sarcoglycan, Sarcospan, Syntrophin.

1. Introduction

Dystrophin is the largest protein isoform expressed from the gene defective in Duchenne muscular dystrophy (Hoffman *et al.*, 1987; Koenig *et al.*, 1988), a lethal muscle-wasting disease that afflicts 1 in 3500 live-born males (Engel, 1986). Based on sequence homology, dystrophin is divided into four distinct domains (Koenig *et al.*, 1988). The amino-terminal 250 residues encode a pair of calponin homology (CH) modules common to several proteins that bind filamentous actin. Adjacent to the amino-terminal domain, more than 2800 amino acids encode 24 homologous triple helical repeats and four hinge domains (Koenig and Kunkel, 1990) that are thought to confer flexibility and elasticity. A third domain of ~400 residues is more complex, encoding a WW module (Bork and Sudol, 1994), two EF hand modules (Koenig *et al.*, 1988), and two ZZ modules in series (Ponting *et al.*, 1996). Finally, the carboxy-terminal ~240 amino acids are unique to dystrophin and its related proteins (Tinsley *et al.*, 1992; Wagner *et al.*, 1993). In total, the four domains of dystrophin are encoded by 3685 amino acids with a molecular weight of 427 kDa.

In skeletal muscle, dystrophin was isolated as part of a large, tightly associated oligomeric complex of proteins synonymously referred to as the dystrophin–glycoprotein complex or dystrophin-associated protein complex (Ervasti *et al.*, 1990; Yoshida and Ozawa, 1990; Ervasti and Campbell, 1991). Investigations into the biological function of the dystrophin–glycoprotein complex suggest it plays an important mechanical function in stabilizing the plasma membrane (the sarcolemma) against stresses imposed during muscle contraction or stretch. The dystrophin–glycoprotein complex has also garnered attention as a putative cellular signaling complex. Here, we review the data supporting current views on the biological function(s) of the dystrophin–glycoprotein complex in striated muscle.

2. Composition of the Core Dystrophin–Glycoprotein Complex

In addition to dystrophin, the core dystrophin–glycoprotein complex contains nine protein subunits encoded by eight different genes. Other proteins include dystroglycans, sarcoglycans, sarcospan, dystrobrevins, and syntrophins. The constituents of the core dystrophin–glycoprotein complex

remain associated in stoichiometric amounts even after multiple purification steps under moderately stringent buffer conditions (Ervasti *et al.*, 1990; Yoshida and Ozawa, 1990; Ervasti and Campbell, 1991). However, several biochemical perturbations further resolve the dystrophin–glycoprotein complex into three subcomplexes (Ervasti and Campbell, 1991; Ervasti *et al.*, 1991; Butler *et al.*, 1992; Yoshida *et al.*, 1994; Kramarcy *et al.*, 1994), each of which will be discussed in greater detail in the following.

2.1. Dystroglycan complex

The dystroglycan subcomplex consists of α- and β-dystroglycan, which are encoded as a single polypeptide from one highly conserved gene (Ibraghimov-Beskrovnaya *et al.*, 1992) that undergoes posttranslational proteolytic cleavage to yield the two tightly (but noncovalently) associated subunits (Ibraghimov-Beskrovnaya *et al.*, 1992; Gee *et al.*, 1993; Smalheiser and Kim, 1995; Deyst *et al.*, 1995; Holt *et al.*, 2000; Esapa *et al.*, 2003; Jayasinha *et al.*, 2003). α-Dystroglycan is an extensively glycosylated extracellular protein (Ervasti and Campbell, 1991, 1993; Gee *et al.*, 1993; Smalheiser and Kim, 1995; Ervasti *et al.*, 1997) consisting of two globular domains connected by an extensible stalk such that α-dystroglycan appears dumbbell shaped when viewed by electron microscopy (Brancaccio *et al.*, 1995, 1997; Bozic *et al.*, 2004; Kunz *et al.*, 2004). Although the chemical makeup of the sugar moieties remains poorly understood, the glycoepitopes on α-dystroglycan mediate binding to components of the extracellular matrix and proper glycosylation is essential to dystroglycan function (Ervasti and Campbell, 1993; Grewal *et al.*, 2001; Michele *et al.*, 2002; Kanagawa *et al.*, 2004; Barresi *et al.*, 2004). β-Dystroglycan is a single-pass transmembrane protein with a largely unstructured amino-terminal extracellular domain that binds to the carboxy-terminal globular domain of α-dystroglycan (Di *et al.*, 1999; Boffi *et al.*, 2001) and a 121-residue carboxy-terminal cytoplasmic domain that binds directly to the WW, EF, and ZZ modules in dystrophin (Suzuki *et al.*, 1992; Jung *et al.*, 1995; Rosa *et al.*, 1996; Rentschler *et al.*, 1999; Chung and Campanelli, 1999; Huang *et al.*, 2000; Ishikawa-Sakurai *et al.*, 2004).

2.2. Sarcoglycan complex

The sarcoglycan/sarcospan subcomplex is composed of α-, β, γ-, and δ-sarcoglycan isoforms, each encoded by a separate gene (Roberds *et al.*, 1993; Lim *et al.*, 1995; Noguchi *et al.*, 1995; Nigro *et al.*, 1996), and sarcospan (Crosbie *et al.*, 1999). All sarcoglycans are single-pass transmembrane glycoproteins with long extracellular domains and relatively short cytoplasmic domains (Roberds *et al.*, 1993; Lim *et al.*, 1995; Noguchi *et al.*, 1995; Nigro *et al.*, 1996). α-Sarcoglycan differs from β-, γ-, and δ-sarcoglycan

in that its amino terminus is oriented extracellularly (Roberds *et al.*, 1993). Sarcospan encodes four transmembrane-spanning segments homologous to the tetraspanin family of proteins (Crosbie *et al.*, 1997), which are thought to mediate interactions between transmembrane proteins. Beyond the four sarcoglycan isoforms initially characterized as a subcomplex of the dystrophin–glycoprotein complex in striated muscle, two additional sarcoglycan genes have been identified. ϵ-Sarcoglycan is most similar in sequence homology and membrane topology to α-sarcoglycan (Ettinger *et al.*, 1997; McNally *et al.*, 1998); it can compensate for the absence of α-sarcoglycan in skeletal muscle (Imamura *et al.*, 2005), but also forms part of a high-molecular-weight complex in muscle that is distinct from the dystrophin–glycoprotein complex (Durbeej *et al.*, 2000). ζ-Sarcoglycan is most homologous to δ- and γ-sarcoglycan (Wheeler *et al.*, 2002), and, accordingly, expression studies in heterologous cells suggest that ζ-sarcoglycan can substitute for γ-sarcoglycan in the sarcoglycan complex (Shiga *et al.*, 2006).

2.3. Dystrobrevin/syntrophin complex

Several studies indicate that dystrophin directly interacts with syntrophins (Butler *et al.*, 1992; Kramarcy *et al.*, 1994; Dwyer and Froehner, 1995; Ahn and Kunkel, 1995; Suzuki *et al.*, 1994, 1995; Yang *et al.*, 1995b; Peters *et al.*, 1997a) and dystrobrevins (Butler *et al.*, 1992; Suzuki *et al.*, 1994; Dwyer and Froehner, 1995; Sadoulet-Puccio *et al.*, 1997; Nawrotzki *et al.*, 1998; Peters *et al.*, 1998), two families of cytoplasmic proteins encoded by multiple genes expressed in a tissue-specific manner (Yang *et al.*, 1994; Ahn *et al.*, 1994, 1996; Adams *et al.*, 1995; Piluso *et al.*, 2000). All syntrophins share a common modular structure consisting of one domain unique to syntrophins, one PDZ domain, and two pleckstrin homology domains that suggest syntrophins function as adaptor proteins involved in anchoring cell signaling molecules to the plasma membrane (Adams *et al.*, 1995; Piluso *et al.*, 2000). The syntrophin unique domain and carboxy-terminal pleckstrin homology domain interact with the extreme carboxy terminus of dystrophin (Ahn and Kunkel, 1995; Suzuki *et al.*, 1995). Of the five known syntrophins, all except γ1 are expressed in skeletal muscle (Peters *et al.*, 1997a; Piluso *et al.*, 2000), but β1 and β2 syntrophins show differences in fiber-type distribution or cellular location that argue for distinct functions (Peters *et al.*, 1997a). Dystrobrevins are so named because they share significant sequence homology with the carboxy-terminal domains of dystrophin (Wagner *et al.*, 1993; Sadoulet-Puccio *et al.*, 1996). Two dystrobrevin genes encode multiple isoforms expressed in a wide array of tissues with α-dystrobrevins expressed predominantly in skeletal muscle (Wagner *et al.*, 1993; Yoshida *et al.*, 1995; Sadoulet-Puccio *et al.*, 1996; Peters *et al.*, 1997b; Blake *et al.*, 1996, 1998; Puca *et al.*, 1998; Holzfeind

et al., 1999). α-Dystrobrevin-1 localizes to the neuromuscular junction while α-dystrobrevin-2 is distributed uniformly throughout the sarcolemma (Peters *et al.*, 1998; Nawrotzki *et al.*, 1998). Pairs of coiled-coil motifs present in α-dystrobrevin and the dystrophin carboxy terminus are responsible for their binding interaction (Sadoulet-Puccio *et al.*, 1997; Peters *et al.*, 1998). In addition to their independent interactions with dystrophin, syntrophins and dystrobrevins directly bind one another (Butler *et al.*, 1992; Dwyer and Froehner, 1995), suggesting that two syntrophin molecules associate with each dystrophin–glycoprotein complex through independent interactions with dystrophin and dystrobrevin. Finally, α-dystrobrevins interact with the sarcoglycan complex (Yoshida *et al.*, 2000), suggesting a role in coupling dystrophin to the glycoprotein complex.

3. Function in Mammals

3.1. Mechanical stabilization and force transmission

While detectable beneath the entire sarcolemma of normal skeletal muscle, dystrophin is particularly concentrated in three subcellular structures implicated in the transmission of contractile force from myofibrils to extracellular elements of muscle tissue. Dystrophin immunostaining is enriched at myotendinous junctions (Fig. 5.1A; Samitt and Bonilla, 1990), and intrafascicular fiber terminations (Paul *et al.*, 2002), which are also referred to as myomuscular junctions (Bassett *et al.*, 2003). Myotendinous and myomuscular junctions are the sites of attachment between the ends of muscle fibers and tendons or serially arranged muscle fibers, respectively, and which

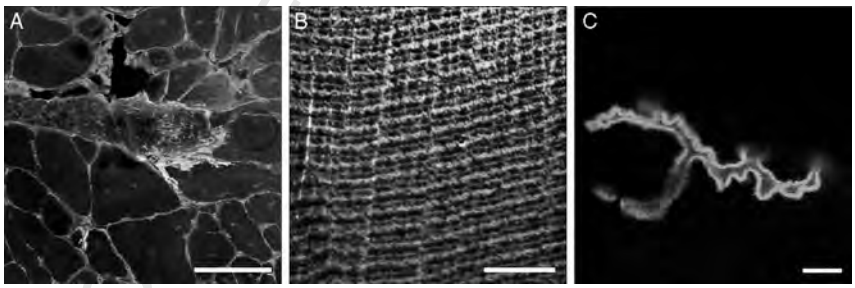

Figure 5.1 Sites of dystrophin–glycoprotein complex enrichment in skeletal muscle. (A) The myotendinous junction identified by immunostaining for tenascin C (green) with individual muscle fibers delineated by immunostaining for laminin (red) and myonuclei (blue) labeled with TO-PRO-3 iodide. Scale bar = 50 μm. (B) Dystrophin immunoreactivity detected at costameres. Scale bar = 10 μm. (C) Neuromuscular junction detected with α-bungarotoxin. Scale bar = 10 μm. (See color insert.)

ultimately transmit the force of muscle fiber contraction to bone. The sarcolemma is highly folded at the myotendinous junction, presumably to increase the surface area contact between muscle fiber ends and tendons. The myotendinous junctions of dystrophin-deficient *mdx* mice are less folded than in wild-type muscle, but also show defective lateral association of terminating sarcomeric thin filaments with the sarcolemma (Tidball and Law, 1991; Law and Tidball, 1993). The dystrophin homologue utrophin is also enriched at myotendinous junctions (Khurana *et al.*, 1991) and mice deficient in both dystrophin and utrophin exhibit more marked reduction in sarcolemmal folding at the myotendinous junction compared to dystrophin-deficient *mdx* mice (Deconinck *et al.*, 1997b).

At nonjunctional regions of the sarcolemma, dystrophin immunostaining displays a rectilinear pattern (Fig. 5.1B) with a major transverse element aligning to myofibrillar Z disks and finer strands aligning with M lines or the long axis of the myofiber (Porter *et al.*, 1992; Straub *et al.*, 1992). The rectilinear lattice is commonly called a costamere, coined from the rib-like appearance of its major Z disk element (Pardo *et al.*, 1983). Clever experiments on carefully dissected bundles of frog myofibers and isolated cardiac myocytes adhered to flexible substrata suggested that costameres physically transmit myofibrillar force across the sarcolemma to the extracellular matrix and adjacent muscle cells (Street, 1983; Danowski *et al.*, 1992). Electron microscopy studies suggested that costameres may also coordinate folding of the sarcolemma during muscle contraction (Street, 1983; Shear and Bloch, 1985). The costameric lattice is disorganized in dystrophin-deficient muscle (Minetti *et al.*, 1992, 1994; Porter *et al.*, 1992; Ehmer *et al.*, 1997; Williams and Bloch, 1999). Costameric disruption is accompanied by greatly increased sarcolemmal fragility/permeability (Mokri and Engel, 1975; Menke and Jockusch, 1991, 1995) resulting in dramatically increased movement of membrane-impermeant molecules across the sarcolemma (Fig. 5.2A; Engel, 1986; Weller *et al.*, 1990; Cox *et al.*, 1993; Clarke *et al.*, 1993; Menke and Jockusch, 1991, 1995; Matsuda *et al.*, 1995; Tinsley *et al.*, 1996; Straub *et al.*, 1997; Vilquin *et al.*, 1998; Harper *et al.*, 2002; Barton *et al.*, 2002; Bansal *et al.*, 2003). Both sarcolemmal permeability and necrosis of dystrophin-deficient muscle are exacerbated by physical exercise and improved by muscle immobilization (Karpati and Carpenter, 1986; Weller *et al.*, 1990; Mizuno, 1992; Clarke *et al.*, 1993; Vilquin *et al.*, 1998; Mokhtarian *et al.*, 1999; Bansal *et al.*, 2003). Thus, enrichments of dystrophin in three structural elements of muscle are important for muscle function, as these structures are perturbed when dystrophin is absent.

Studies using noninvasive assays that measure the pulling force or grip strength of intact alert animals have demonstrated that dystrophin-deficient *mdx* mice are weak (Carlson and Makiejus, 1990; Tinsley *et al.*, 1998; Connolly *et al.*, 2001; Sonnemann *et al.*, 2006). Because muscle-specific expression of the dystrophin homologue utrophin in *mdx* mice restored

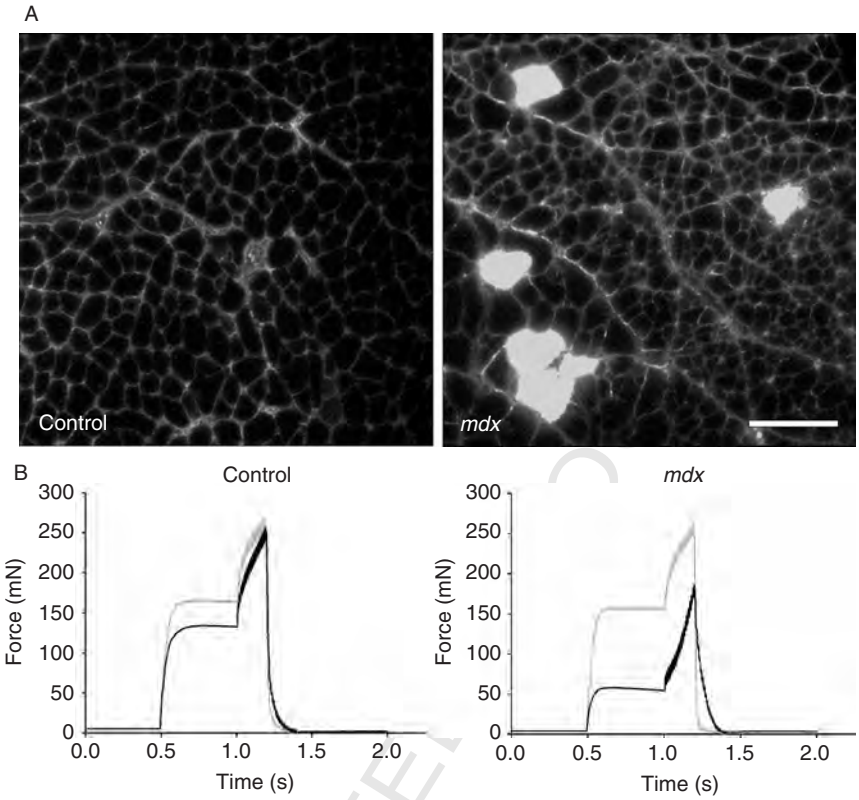

Figure 5.2 **Dystrophin-deficient muscle exhibits increased sarcolemmal permeability and contraction-induced injury. (A) Infiltration of membrane-impermeant Evans blue dye (red) into muscle fibers of dystrophin-deficient *mdx* muscle but not wild-type control muscle. Scale bar = 100 μm. (B) Tetanic force is significantly depressed from the first (red) to the fifth (black) eccentric contraction in extensor digitorum longus muscles from dystrophin-deficient *mdx* mice compared to control. (See color insert.)**

muscle strength to normal values (Tinsley *et al.*, 1998), it is likely that the primary cause of weakness is due to the absence of dystrophin from skeletal muscle and not from a nervous tissue defect. Numerous *ex vivo* studies confirm that dystrophin-deficient muscle is weak, particularly when force output is normalized against muscle cross-sectional area (Coulton *et al.*, 1988; Kometani *et al.*, 1990; Stedman *et al.*, 1991; Sacco *et al.*, 1992; Quinlan *et al.*, 1992; Cox *et al.*, 1993; Pastoret and Sebille, 1993; Tinsley *et al.*, 1998; Deconinck *et al.*, 1997c, 1998; Bobet *et al.*, 1998; Stevens and Faulkner, 2000; Lynch *et al.*, 2001; DelloRusso *et al.*, 2001; Harper *et al.*, 2002; Barton *et al.*, 2002). Although the molecular basis for muscle weakness associated with dystrophin deficiency has been elusive, it seems not to involve a defect in sarcomeric force production (Lynch *et al.*, 2000; Lowe

et al., 2006) but may be due in part to defective force transmission at the myotendinous junction (Deconinck *et al.*, 1997b). While excitation–contraction coupling is not altered, calcium release from the sarcoplasmic reticulum is significantly decreased in *mdx* myofibers, which also likely contributes to the observed force deficit (Woods *et al.*, 2004, 2005).

In addition to decreased normalized force production, dystrophin-deficient muscle is hypersensitive to lengthening (eccentric) contractions (Fig. 5.2B). When *mdx* muscle is forcibly lengthened during tetanic stimulation, force production is immediately and dramatically reduced (Petrof *et al.*, 1993; Moens *et al.*, 1993; Brooks, 1998; DelloRusso *et al.*, 2001). Consistent with a role in sarcolemmal stability, the drop in force generated by intact dystrophin-deficient muscle after experiencing eccentric contraction is well correlated with increased sarcolemmal permeability (Petrof *et al.*, 1993; Moens *et al.*, 1993; Deconinck *et al.*, 1996, 1997c, 1998; Brooks, 1998; Tinsley *et al.*, 1998; DelloRusso *et al.*, 2001; Harper *et al.*, 2002; Barton *et al.*, 2002). In contrast, permeabilized dystrophin-deficient myofibers are neither weaker nor more sensitive to eccentric contraction compared to controls (Lynch *et al.*, 2000).

Knockout of the dystroglycan or sarcoglycan subcomplexes also causes muscular dystrophy that is accompanied by defects in sarcolemmal integrity (Duclos *et al.*, 1998; Araishi *et al.*, 1999; Coral-Vazquez *et al.*, 1999; Cote *et al.*, 1999; Hack *et al.*, 1998, 2000; Durbeej *et al.*, 2000; Straub *et al.*, 2000; Cohn *et al.*, 2002; Sasaoka *et al.*, 2003). Genetic ablation of individual sarcoglycan genes results in a progressive muscular dystrophy phenotype associated with loss of expression of the other three sarcoglycan proteins and sarcospan (Duclos *et al.*, 1998; Araishi *et al.*, 1999; Durbeej *et al.*, 2000; Coral-Vazquez *et al.*, 1999; Hack *et al.*, 1998, 2000; Sasaoka *et al.*, 2003) while knockout of sarcospan caused no apparent muscle phenotype or effect on sarcoglycan complex expression (Lebakken *et al.*, 2000). Because the biochemical stability of the dystrophin–glycoprotein complex is greatly impaired in sarcoglycan-deficient muscle (Duclos *et al.*, 1998; Araishi *et al.*, 1999; Durbeej *et al.*, 2000), the sarcoglycan complex is thought to play a role in stabilizing the linkages formed by β-dystroglycan with α-dystroglycan and dystrophin.

Dystrophin is also enriched in costameres and intercalated disks of cardiac muscle (Kaprielian *et al.*, 2000). Like skeletal muscle, dystrophin-deficient cardiac myocytes are abnormally vulnerable to mechanical stress-induced injury and contractile failure (Danialou *et al.*, 2001; Kamogawa *et al.*, 2001; Yasuda *et al.*, 2005). Interestingly, treatment with chemical-based membrane sealants was shown to correct the cardiac defects associated with dystrophin deficiency in mice (Yasuda *et al.*, 2005). Finally, coxsackie B virus infection results in dilated cardiomyopathy and a virally expressed protease specifically cleaves dystrophin (Badorff *et al.*, 1999, 2000) and is sufficient to induce dilated cardiomyopathy (Xiong *et al.*, 2007).

When taken together, the previous studies indicate that one primary function of the dystrophin–glycoprotein complex is to stabilize muscle cells, and particularly the sarcolemma, against mechanical forces transduced through costameres during muscle contraction or stretch.

While the impressive biochemical stability of the dystrophin–glycoprotein complex combined with the loss of sarcolemmal integrity when it is absent or defective strongly supports a role in mechanical stabilization, the complex does not function in isolation but instead through collaboration with several other cellular constituents. *In vitro* studies demonstrated that spectrin repeat 2 of the large dystrophin rod domain binds strongly to phospholipids, which may modify the physical properties of the sarcolemmal lipid bilayer and/or associated proteins (DeWolf *et al.*, 1997; Le *et al.*, 2003). In support of a role for phospholipid binding *in vivo*, truncated dystrophin transgenes lacking spectrin repeats 2 and 3 were less effective in rescuing the phenotype of dystrophin-deficient *mdx* mice compared to constructs containing these repeats, although substitution of hinge 2 with hinge 3 also complicated the interpretation (Harper *et al.*, 2002).

Several studies have demonstrated that dystrophin purified from a variety of tissues can bind actin filaments *in vitro* with submicromolar affinity (Ervasti and Campbell, 1993; Fabbrizio *et al.*, 1993; Senter *et al.*, 1993; Lebart *et al.*, 1995; Rybakova *et al.*, 1996). *In vivo*, dystrophin interacts with actin filaments composed of the nonmuscle γ-actin isoform (Rybakova *et al.*, 2000; Ursitti *et al.*, 2004), which concentrates primarily at the sarcolemma and particularly within costameres (Craig and Pardo, 1983; Rybakova *et al.*, 2000; Hanft *et al.*, 2006; Sonnemann *et al.*, 2006). Studies aimed at identifying the actin-binding sites within dystrophin have confirmed an important contribution by the amino-terminal, tandem calponin homology domain (Hemmings *et al.*, 1992; Way *et al.*, 1992; Fabbrizio *et al.*, 1993; Corrado *et al.*, 1994; Jarrett and Foster, 1995; Rybakova *et al.*, 1996), but also identified a second actin-binding domain encoded by a cluster of basic spectrin repeats located in the middle rod domain of dystrophin (Rybakova *et al.*, 1996; Rybakova and Ervasti, 1997; Amann *et al.*, 1998, 1999). Although either actin-binding domain is sufficient to physically anchor costameric actin filaments to the sarcolemma (Warner *et al.*, 2002; Hanft *et al.*, 2006), the amino-terminal actin-binding domain appears to be more important from a functional perspective (Warner *et al.*, 2002; Harper *et al.*, 2002). α-Syntrophin also binds actin filaments *in vitro* (Iwata *et al.*, 1998, 2004), which suggests it may contribute to the actin-binding activity of the dystrophin–glycoprotein complex (Rybakova *et al.*, 1996). However, more recent quantitative comparisons of the actin-binding properties of full-length recombinant dystrophin with those measured for the dystrophin–glycoprotein complex indicate that dystrophin alone can account for all actin-binding activity of the complex (Rybakova

et al., 2006). Through direct interaction with the sarcoglycan complex (Thompson *et al.*, 2000), filaminC forms yet another linkage between the dystrophin–glycoprotein complex and the actin cytoskeleton. Like dystrophin, filamins contain an amino-terminal tandem calponin homology actin-binding domain but encode 24 immunoglobulin G (IgG) motifs rather than spectrin-type repeats (Stossel *et al.*, 2001). The phenotype of mice ablated for filaminC expression indicates that filaminC plays a crucial role in maintaining muscle structure (Dalkilic *et al.*, 2006).

In addition to interactions with the actin cytoskeleton, multiple studies have demonstrated an association of the dystrophin–glycoprotein complex with the intermediate filament cytoskeleton through several distinct pathways. First, two-hybrid screens and subsequent experiments identified desmuslin/synemin (Mizuno *et al.*, 2001) and syncoilin (Newey *et al.*, 2001; Poon *et al.*, 2002) as two proteins that couple α-dystrobrevin of the dystrophin–glycoprotein complex with the intermediate filament desmin. More recent biochemical studies have demonstrated the ability of desmuslin/synemin to directly bind sequences within the middle rod and WW/EF/ZZ domains of dystrophin (Bhosle *et al.*, 2006). Dystrophin also associates with cytokeratins 8 and 19 at costameres through a direct interaction of keratin 19 with the amino-terminal, tandem calponin homology domain of dystrophin (O'Neill *et al.*, 2002; Ursitti *et al.*, 2004; Stone *et al.*, 2005). Most recently, an isoform of the giant cytolinker plectin has been localized to the sarcolemma and costameres of skeletal muscle and was demonstrated to directly bind dystrophin and β-dystroglycan (Rezniczek *et al.*, 2007), which provides yet another mechanical linkage between the dystrophin–glycoprotein complex, the actin cytoskeleton, and the intermediate filament lattice. In conclusion, dystrophin, β-dystroglycan, α-dystrobrevin, and sarcoglycans all appear to couple the dystrophin–glycoprotein complex to other structural elements, which provides additional support for an essential structural/mechanical role in striated muscle.

On the external surface of the sarcolemma, components of the dystrophin–glycoprotein complex have been shown to interact with several constituents of the extracellular matrix. Through its incompletely characterized carbohydrate epitopes (Section 2.1), α-dystroglycan has been shown to interact with laminins (Ibraghimov-Beskrovnaya *et al.*, 1992; Ervasti and Campbell, 1993), agrins (Bowe *et al.*, 1994; Campanelli *et al.*, 1994; Gee *et al.*, 1994; Sugiyama *et al.*, 1994), and perlecan (Talts *et al.*, 1999; Peng *et al.*, 1999; Kanagawa *et al.*, 2005), which all bind α-dystroglycan through a conserved G-domain motif (Gee *et al.*, 1993; Hohenester *et al.*, 1999). Laminin-2 is the predominant laminin isoform expressed in striated muscle (Patton *et al.*, 1997) and mutations leading to laminin-2 deficiency cause forms of congenital muscular dystrophy (Xu *et al.*, 1994; Sunada *et al.*, 1994; Helbling-Leclerc *et al.*, 1995). Unlike dystrophies caused by defects in the dystrophin–glycoprotein complex, laminin-2-deficient muscular dystrophy

is not associated with compromised sarcolemmal integrity (Straub *et al.*, 1997), but instead involves muscle cell apoptosis in its pathomechanism (Girgenrath *et al.*, 2004; Dominov *et al.*, 2005). While dystroglycan binding to agrin and perlecan has been most extensively studied at the neuromuscular junction (Section 3.2), it bears noting that transgenic expression of agrin minigenes (Moll *et al.*, 2001) or agrin/perlecan chimeras (Meinen *et al.*, 2007) can rescue the dystrophic phenotype of laminin-2-deficient muscle. These results suggest that dystroglycan plays an important role in anchoring muscle cells to the extracellular matrix. While strong, the mechanical linkages between the basement membrane, the dystrophin–glycoprotein complex, and the costameric cytoskeleton are not static and unchanging as denervation causes rapid reorientation of costameres and the laminin-2 matrix from a transverse to a longitudinal pattern (Bezakova and Lomo, 2001). Moreover, it appears that agrin isoforms secreted by muscle cells are important for the maintenance of costamere organization because the transverse to a longitudinal reorientation after denervation was prevented by exogenous application of muscle agrin (Bezakova and Lomo, 2001). More recently, experiments demonstrated that biglycan, a small proteoglycan, binds to α-dystroglycan (Bowe *et al.*, 2000) and α- and γ-sarcoglycans (Rafii *et al.*, 2006). Biglycan null mice display a mild dystrophic phenotype and a subpopulation of muscle fibers shows evidence of impaired sarcolemmal integrity (Mercado *et al.*, 2006), suggesting it may stabilize links between the dystroglycan and sarcoglycan complexes and between the sarcoglycan complex and the extracellular matrix. However, the loss of α-dystrobrevin isoforms in biglycan null muscle may have also contributed to the dystrophic phenotype (Mercado *et al.*, 2006).

Finally, a structural/mechanical role for the dystrophin–glycoprotein complex is supported by examining how muscle responds to the loss of dystrophin. Several structural proteins of costameres, myotendinous and/or myomuscular junctions are upregulated in *mdx* muscle including talin and vinculin (Law *et al.*, 1994), $\alpha_7\beta_1$ integrin (Vachon *et al.*, 1997; Hodges *et al.*, 1997), plectin (Schroder *et al.*, 1997; Rezniczek *et al.*, 2007), filaminC (Thompson *et al.*, 2000), biglycan (Bowe *et al.*, 2000), dysbindin (Benson *et al.*, 2001), syncoilin (Newey *et al.*, 2001), and cytoplasmic γ-actin (Hanft *et al.*, 2006). While targeted to the neuromuscular and myotendinous junctions in adult muscle (Khurana *et al.*, 1991; Ohlendieck *et al.*, 1991), utrophin expression is increased in dystrophin-deficient muscle (Matsumura *et al.*, 1992; Porter *et al.*, 1998) and is redirected to costameres (Williams and Bloch, 1999; Rybakova *et al.*, 2000, 2002). These data suggest that dystrophin-deficient muscle responds to mechanical instability through compensatory remodeling of the cytoskeleton. Moreover, transgenic overexpression of α_7 integrin (Burkin *et al.*, 2001) or utrophin (Tinsley *et al.*, 1998) results in partial to complete rescue of the dystrophic phenotype. In summary, the proteins upregulated in response to dystrophin deficiency

are capable of compensating for the missing physical linkage between the sarcolemma and myofibrillar apparatus and thus support a mechanical function for the dystrophin–glycoprotein complex.

3.2. Organization and stabilization of the neuromuscular junction

The dystrophin–glycoprotein complex is also enriched at the motor end plate of the neuromuscular junction (Fig. 5.1C). However, differences in molecular composition and subcellular distribution suggest its function at this important site of nerve/muscle communication may vary as well. A dystrophin–glycoprotein complex with molecular composition very similar to that expressed throughout the extrasynaptic sarcolemma and costameres is localized to the deep troughs of the junctional folds (Byers *et al.*, 1991; Sealock *et al.*, 1991; Peters *et al.*, 1998). At the crests of junctional folds, dystrophin is replaced by its close homologue utrophin and the longer α-dystrobrevin-1 isoform replaces the shorter α-dystrobrevin-2 isoform that predominates in the extrasynaptic dystrophin–glycoprotein complex (Peters *et al.*, 1998). As noted earlier, β_2-syntrophin is exclusively localized to the neuromuscular junction (Peters *et al.*, 1997a).

Interest in the role of the dystrophin/utrophin–glycoprotein complex in neuromuscular synaptogenesis was piqued by reports from several laboratories that α-dystroglycan bound with high affinity to agrin (Bowe *et al.*, 1994; Campanelli *et al.*, 1994; Gee *et al.*, 1994; Sugiyama *et al.*, 1994), an interaction that induces high-density clustering of acetylcholine receptors at the motor end plate (Gautam *et al.*, 1996). Furthermore, β-dystroglycan was shown to directly bind rapsyn (Cartaud *et al.*, 1998; Bartoli *et al.*, 2001), a cytoplasmic protein that is required for acetylcholine receptor clustering in muscle (Apel *et al.*, 1997). However, agrin can induce acetylcholine receptor clustering in dystroglycan null myotubes (Grady *et al.*, 2000), leaving the physiological relevance of agrin binding to α-dystroglycan at the neuromuscular junction unclear. Perlecan binding to α-dystroglycan, on the other hand, has been implicated in anchoring acetylcholinesterase to the neuromuscular junction (Peng *et al.*, 1999; Arikawa-Hirasawa *et al.*, 2002). Genetic ablation of dystrophin (Lyons and Slater, 1991; Grady *et al.*, 1997b), utrophin (Grady *et al.*, 1997a; Deconinck *et al.*, 1997a), α-syntrophin (Adams *et al.*, 2000) or β_1-syntrophin (Adams *et al.*, 2004), α-dystrobrevin (Grady *et al.*, 2000), or dystroglycan (Cote *et al.*, 1999) all caused morphological abnormalities in the neuromuscular junction. Similarly, the density of acetylcholine receptors at the neuromuscular junction is significantly decreased in mice lacking α-dystrobrevin (Grady *et al.*, 2000; Akaaboune *et al.*, 2002) or α-syntrophin (Adams *et al.*, 2000), suggesting that the dystrophin/utrophin–glycoprotein complex contributes to the long-term stability of functionally important elements in the motor end plate.

While α-dystrobrevin and dystroglycan null animals present with muscular dystrophy (Grady *et al.*, 1999; Cote *et al.*, 1999; Cohn *et al.*, 2002), utrophin and syntrophin null animals are phenotypically normal (Grady *et al.*, 1997a; Deconinck *et al.*, 1997a), and dystrophic α-dystrobrevin null mice can be rescued by transgenic expression of α-dystrobrevin-2 without restoring neuromuscular junction morphology (Grady *et al.*, 2003). These data suggest that morphological defects in the neuromuscular junction do not contribute significantly to pathologies associated with absence or abnormality in the dystrophin–glycoprotein complex.

3.3. Cellular signaling

Through syntrophins, the dystrophin–glycoprotein complex is thought to anchor a variety of signaling molecules near their sites of action. Neuronal nitric oxide synthase (nNOS) was first shown to copurify with the dystrophin–glycoprotein complex (Brenman *et al.*, 1995) through a direct interaction with α-syntrophin (Adams *et al.*, 2001). Syntrophins have since been found to bind a variety of channels (Gee *et al.*, 1998; Adams *et al.*, 2001; Vandebrouck *et al.*, 2007), kinases (Lumeng *et al.*, 1999; Abramovici *et al.*, 2003), and kinase substrates (Luo *et al.*, 2005). Because nNOS localization to the sarcolemma and enzymatic activity were disrupted in dystrophin-deficient *mdx* mice (Brenman *et al.*, 1995), it was hypothesized that aberrant nNOS regulation may importantly contribute to the muscle degeneration accompanying dystrophinopathy. However, genetic ablation of nNOS did not induce a muscular phenotype in mice (Huang *et al.*, 1993). Furthermore, transgenic expression of a truncated dystrophin (Harper *et al.*, 2002) or full-length utrophin (Tinsley *et al.*, 1998) fully reversed muscular dystrophy in *mdx* mice without restoring sarcolemmal nNOS (Judge *et al.*, 2006; Yokota *et al.*, 2006). Finally, mice knocked out for α-syntrophin (Kameya *et al.*, 1999; Adams *et al.*, 2000), β_2-syntrophin (Adams *et al.*, 2004), or both genes (Adams *et al.*, 2004) exhibited no evidence of muscle disease. Thus, it appears that the loss of signal-molecule anchoring function plays no primary role in causing dystrophin-deficient muscular dystrophy, although it may contribute to secondary disease features such as impaired vascular perfusion during muscle contraction (Sander *et al.*, 2000; Thomas *et al.*, 1998, 2003), altered muscle regeneration (Anderson, 2000; Hosaka *et al.*, 2002), inflammation (Wehling *et al.*, 2001), or oxidative stress (Dudley *et al.*, 2006).

The dystrophin–glycoprotein complex is also hypothesized to directly regulate the mitogen-activated protein (MAP) kinase and AKT signaling pathways in skeletal muscle (Rando, 2001; Batchelor and Winder, 2006). Early studies in support of this hypothesis documented *in vitro* binding of β-dystroglycan (Yang *et al.*, 1995a) and syntrophin (Oak *et al.*, 2001) to Grb2, an adaptor protein containing Src homology 2 and 3 domains that

couples receptor tyrosine kinases to MAP kinase cascades via small GTPase family members. More recent *in vitro* experiments have led one group to propose that laminin binding to α-dystroglycan induces assembly of a syntrophin–Grb2–Sos1–Rac1–Pak1–JNK complex initiated by tyrosine phosphorylation of syntrophin and resulting in JNK activation (Oak *et al.*, 2003; Zhou *et al.*, 2006). Another group has reported that β-dystroglycan can directly bind either MEK or ERK alone *in vitro*, leading the authors to hypothesize that it serves a scaffold function important for MAP kinase signaling (Spence *et al.*, 2004). The relevance of both stories (Zhou *et al.*, 2006; Spence *et al.*, 2004) to the *in vivo* function of the dystrophin–glycoprotein complex remains to be demonstrated. In neither case have the signaling molecules actually been shown to interact with the fully assembled dystrophin–glycoprotein complex expressed in striated muscle. As noted previously, mice null for α-syntrophin (Kameya *et al.*, 1999; Adams *et al.*, 2000), β_2-syntrophin (Adams *et al.*, 2004), or both genes (Adams *et al.*, 2004) exhibited no muscular dystrophy. Furthermore, the dystrophic phenotype of *mdx* mice was not improved by transgenic over-expression of dystroglycan (Hoyte *et al.*, 2004), Dp71 (Cox *et al.*, 1994; Greenberg *et al.*, 1994), or Dp116 (Judge *et al.*, 2006) even though the dystrophin–glycoprotein complex constituents necessary for signaling were restored to the sarcolemma.

To investigate a potential role for the dystrophin–glycoprotein complex in MAP kinase signaling *in vivo*, a number of groups have compared MAP kinase activity in muscle from wild-type and dystrophic mice lacking either dystrophin or γ-sarcoglycan (Kolodziejczyk *et al.*, 2001; Kumar *et al.*, 2004; Lang *et al.*, 2004; Nakamura *et al.*, 2001, 2002, 2005; Griffin *et al.*, 2005; Barton, 2006). Results have differed dramatically across studies even when the same MAP kinase was evaluated in the same animal model. Three studies found no difference in activated ERK1/2 of resting *mdx* muscle (Kolodziejczyk *et al.*, 2001; Nakamura *et al.*, 2005; Kumar *et al.*, 2004) while three others reported increased ERK1/2 activation in *mdx* muscle (Nakamura *et al.*, 2001, 2002; Barton, 2006). The activity of p38 in *mdx* muscle was not altered in four studies (Kolodziejczyk *et al.*, 2001; Kumar *et al.*, 2004; Nakamura *et al.*, 2005; Lang *et al.*, 2004), but was elevated in two others (Nakamura *et al.*, 2001, 2002). JNK1 was elevated in *mdx* in one study (Kolodziejczyk *et al.*, 2001) but was not found to be different from control in four others (Nakamura *et al.*, 2001, 2002, 2005; Kumar *et al.*, 2004). Even after taking into account the variation in animal ages and muscles analyzed, it is difficult to draw any firm conclusions over how defects in the dystrophin–glycoprotein complex may affect MAP kinase signaling. The results of several studies further suggest that a mechanotransduction pathway impinging on MAP kinase activation may be perturbed in muscle expressing a defective dystrophin–glycoprotein complex (Nakamura *et al.*, 2005; Kumar *et al.*, 2004; Griffin *et al.*, 2005; Barton, 2006), yet even

some of these data appear contradictory. ERK1/2 became more activated in stretched/exercised *mdx* muscle in two studies (Kumar *et al.*, 2004; Nakamura *et al.*, 2005), but activity was reduced by eccentric contraction in a third (Barton, 2006). Stretch had opposite effects on ERK1/2 activity when compared across two studies of γ-sarcoglycan null muscle (Griffin *et al.*, 2005; Barton, 2006). Finally, the activity of p38 was significantly enhanced in exercised *mdx* muscle (Nakamura *et al.*, 2005) but not in *mdx* muscle that was acutely stretched (Kumar *et al.*, 2004).

Toward a role for the dystrophin–glycoprotein complex in regulating Akt signaling in skeletal muscle, one group reported that disruption of laminin binding to α-dystroglycan induced apoptosis in cultured myotubes accompanied by decreased Akt activity (Langenbach and Rando, 2002). It was suggested that loss of dystrophin–glycoprotein complex function may impair cell survival signaling through the Akt pathway with enhanced apoptosis contributing to dystrophic pathogenesis. However, two new studies have paradoxically reported elevated Akt activity in dystrophin-deficient *mdx* muscle (Dogra *et al.*, 2006; Peter and Crosbie, 2006). Moreover, transgenic overexpression of the antiapoptosis proteins ARC (Abmayr *et al.*, 2004) and BCL2 (Dominov *et al.*, 2005) failed to alleviate dystrophy in *mdx* muscle. Thus, it remains to be demonstrated that the dystrophin–glycoprotein complex directly regulates a signal transduction pathway or that its disruption directly alters muscle cell signaling in a manner that contributes substantively to the pathologies observed in dystrophic mammalian muscle. Alternatively, aberrant signaling may be an adaptive response by dystrophin-deficient muscle attempting to maintain homeostasis, or more interestingly, may be an adverse consequence of cytoskeletal remodeling (Rezniczek *et al.*, 2007).

4. Function in Model Organisms

4.1. Caenorhabditis elegans

Of three popular model organisms interrogated, the function of the dystrophin–glycoprotein complex is best understood in the nematode worm, *Caenorhabditis elegans*. The *C. elegans* genome encodes genes for dystrophin/utrophin (*dys-1)*, dystroglycan (*dgn-1)*, sarcoglycans, dystrobrevins (*dyb-1)*, and syntrophins (*stn-1)* (Bessou *et al.*, 1998; Gieseler *et al.*, 1999, 2001; Grisoni *et al.*, 2002, 2003). Mutations or RNAi that target each gene similarly cause a mild phenotype characterized by exaggerated head bending, hyperactivity, and hypercontractility (Bessou *et al.*, 1998; Gieseler *et al.*, 1999, 2001; Grisoni *et al.*, 2002, 2003). Mutations in *dys-1, dyb-1,* and *stn-1* also show increased sensitivity to acetylcholine and the acetylcholinesterase inhibitor aldicarb, which suggested that the motility phenotypes

were due to altered cholinergic signaling (Bessou *et al.*, 1998; Gieseler *et al.*, 1999, 2001; Grisoni *et al.*, 2003). In support of this hypothesis, the *snf-6* gene encodes a novel acetylcholine transporter localized to the motor end plate of the *C. elegans* neuromuscular junction, snf-6 binds to stn-1, and *snf-6* mutations phenocopy *dys-1, dyb-1*, and *stn-1* mutants (Kim *et al.*, 2004). Ablation of *dys-1* (Gieseler *et al.*, 2000), *dyb-1* (Gieseler *et al.*, 2001), or *snf-6* (Kim *et al.*, 2004) combined with a mildly affected mutant of *MyoD* (*hlh-1)* causes a more severe, muscle degeneration phenotype consistent with the more severely affected *mdx/MyoD*$^{-/-}$ double knockout mice (Megeney *et al.*, 1999). Furthermore, microarray comparisons between wild-type and *dys-1* mutants revealed altered transcript profiles (Towers *et al.*, 2006) comparable to the differences reported for patients with Duchenne muscular dystrophy (Chen *et al.*, 2000). Interestingly, mutations that slightly impair contractility at several steps downstream of nerve–muscle communication can suppress muscle degeneration in *dys-1/hlh-1* double mutants (Mariol *et al.*, 2007). Thus, it appears that the dystrophin–glycoprotein complex in *C. elegans* primarily functions to localize a protein (snf-6) important for termination of neuromuscular transmission and when disrupted, hypercontractility can initiate muscle degeneration on a sensitized background. Finally, the phenotype of *dyc-1* mutants resembles that of *dys-1* mutants and dyc-1 overexpression partially suppresses the *dys-1* phenotype (Gieseler *et al.*, 2000). *dyc-1* is homologous with mammalian CAPON, which interacts with neuronal nitric oxide synthase through its PDZ domain (Gieseler *et al.*, 2000) and is upregulated in dystrophin-deficient *mdx* muscle (Segalat *et al.*, 2005). Thus, studies in *C. elegans* may help explain why defects in the dystrophin–glycoprotein complex cause perturbations in the neuromuscular junction without apparent functional consequence in mammals (Section 3.2).

4.2. Drosophila

As in *C. elegans*, the *Drosophila* genome encodes homologues for dystrophin, dystroglycan, dystrobrevin, sarcoglycans, and syntrophin (Roberts and Bobrow, 1998; Neuman *et al.*, 2001; Greener and Roberts, 2000). Consistent with studies in mammals (Section 3) and worms (Section 4.1), genetic and RNAi-mediated knockdown of dystrophin or dystroglycan in *Drosophila* causes decreased mobility and age-dependent muscle degeneration (Shcherbata *et al.*, 2007). Also like *C. elegans, Drosophila* mutants lacking a large dystrophin isoform localized to the neuromuscular junction show enhanced neuromuscular transmission, but through elevated release of neurotransmitter from presynaptic sites (van der Plas *et al.*, 2006) rather than impaired postsynaptic uptake as found in the worm (Kim *et al.*, 2004). Interestingly, a hypercontraction-induced myopathy has been described in

Drosophila with mutations in the myosin heavy chain (*mhc*) locus (Montana and Littleton, 2004). While not directly relevant to dystrophin–glycoprotein complex function, comparison of transcript expression profiles of *Drosophila mhc* mutants with those from mammalian dystrophies suggested that compensatory cytoskeletal remodeling may be a common response to muscle disease that is conserved across species (Montana and Littleton, 2006).

4.3. Zebrafish

The small vertebrate zebrafish (*Danio rerio*) has emerged as a model system to study the function of the dystrophin–glycoprotein complex. Orthologs for dystrophin, dystroglycan, dystrobrevin, and sarcoglycans have been identified in zebrafish through a variety of approaches (Parsons *et al.*, 2002; Guyon *et al.*, 2003; Bassett *et al.*, 2003; Jin *et al.*, 2007; Steffen *et al.*, 2007). Ablation of dystrophin or dystroglycan results in loss of stable muscle attachments analogous to the myotendinous or myomuscular junction in mammals, impaired muscle integrity, and necrosis (Parsons *et al.*, 2002; Bassett *et al.*, 2003). A more recent study further identified an important role for dystroglycan in the formation of distributed neuromuscular synapses as opposed to the focal neuromuscular junctions almost exclusively studied in mammals (Lefebvre *et al.*, 2007). Most interestingly, a zebrafish mutant in the nicotinic acetylcholine receptor (*sofa potato*) was shown to suppress myopathy associated with dystrophin deficiency but did not suppress the myopathy caused by dystroglycan ablation (Etard *et al.*, 2005), similar to conclusions that emerged from a study of the zebrafish *candyfloss* mutant, a model of laminin-2-deficient muscular dystrophy (Hall *et al.*, 2007). These studies suggest that decreased contractility can reduce mechanically induced injury in dystrophin-deficient muscle, but they also suggest that the absence of dystrophin and dystroglycan induces different mechanisms of pathogenesis. In summary, the zebrafish is emerging as the model organism that may best recapitulate the functional deficits associated with dystrophin–glycoprotein complex abnormalities in mammals (Section 3), and that may also provide the most insight into poorly understood functions of the complex.

5. Concluding Remarks

In comparing the studies in mammals (Section 3) with model organisms (Section 4), we notice two distinct but interrelated pathways to muscle degeneration associated with defects in the dystrophin–glycoprotein complex. First, the cytoskeletal framework of muscle may be compromised to the point that it cannot protect muscle cells against the normal forces generated within. In the second pathway, defects lead to excessive force

production that appears to overwhelm an otherwise normal cytoskeletal support structure. In both cases, there are indications that dystrophic muscle attempts to compensate through cytoskeletal remodeling. It also seems likely that the dystrophin–glycoprotein complex plays multiple roles in mammalian muscle but that some model organisms may employ the complex for fewer, and perhaps only one function. In conclusion, comparing and contrasting results of dystrophin–glycoprotein complex studies across a wide range of organisms promises not only to shed light on its versatility, but also on secondary functions that are difficult to address solely in mammals.

ACKNOWLEDGMENTS

The authors thank members of the Ervasti laboratory for their helpful feedback on this review and particularly Michele Jaeger for providing images in Fig. 5.1. Supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR042423 and AR049899), the Muscular Dystrophy Association, the Foundation to Eradicate Duchenne, the Nash Avery Foundation, and Charley's Fund.

REFERENCES

Abmayr, S., Crawford, R. W., and Chamberlain, J. S. (2004). Characterization of ARC, apoptosis repressor interacting with CARD, in normal and dystrophin-deficient skeletal muscle. *Hum. Mol. Genet.* **13,** 213–221.

Abramovici, H., Hogan, A. B., Obagi, C., Topham, M. K., and Gee, S. H. (2003). Diacylglycerol kinase-zeta localization in skeletal muscle is regulated by phosphorylation and interaction with syntrophins. *Mol. Biol. Cell* **14,** 4499–4511.

Adams, M. E., Dwyer, T. M., Dowler, L. L., White, R. A., and Froehner, S. C. (1995). Mouse α1- and β2-syntrophin gene structure, chromosome localization, and homology with a discs large domain. *J. Biol. Chem.* **270,** 25859–25865.

Adams, M. E., Kramarcy, N., Krall, S. P., Rossi, S. G., Rotundo, R. L., Sealock, R., and Froehner, S. C. (2000). Absence of α-syntrophin leads to structurally aberrant neuromuscular synapses deficient in utrophin. *J. Cell Biol.* **150,** 1385–1398.

Adams, M. E., Mueller, H. A., and Froehner, S. C. (2001). *In vivo* requirement of the α-syntrophin PDZ domain for the sarcolemmal localization of nNOS and aquaporin-4. *J. Cell Biol.* **155,** 2–10.

Adams, M. E., Kramarcy, N., Fukuda, T., Engel, A. G., Sealock, R., and Froehner, S. C. (2004). Structural abnormalities at neuromuscular synapses lacking multiple syntrophin isoforms. *J. Neurosci.* **24,** 10302–10309.

Ahn, A. H., and Kunkel, L. M. (1995). Syntrophin binds to an alternatively spliced exon of dystrophin. *J. Cell Biol.* **128,** 363–371.

Ahn, A. H., Yoshida, M., Anderson, M. S., Feener, C. A., Selig, S., Hagiwara, Y., Ozawa, E., and Kunkel, L. M. (1994). Cloning of human basic A1, a distinct 59-kDa dystrophin-associated protein encoded on chromosome 8q23–24. *Proc. Natl. Acad. Sci. USA* **91,** 4446–4450.

Ahn, A. H., Freener, C. A., Gussoni, E., Yoshida, M., Ozawa, E., and Kunkel, L. M. (1996). The three human syntrophin genes are expressed in diverse tissues, have distinct

chromosomal locations, and each binds to dystrophin and its relatives. *J. Biol. Chem.* **271,** 2724–2730.

Akaaboune, M., Grady, R. M., Turney, S., Sanes, J. R., and Lichtman, J. W. (2002). Neurotransmitter receptor dynamics studied *in vivo* by reversible photo-unbinding of fluorescent ligands. *Neuron* **34,** 865–876.

Amann, K. J., Renley, B.A, and Ervasti, J. M. (1998). A cluster of basic repeats in the dystrophin rod domain binds F-actin through an electrostatic interaction. *J. Biol. Chem.* **273,** 28419–28423.

Amann, K. J., Guo, W. X. A., and Ervasti, J. M. (1999). Utrophin lacks the rod domain actin binding activity of dystrophin. *J. Biol. Chem.* **274,** 35375–35380.

Anderson, J. E. (2000). A role for nitric oxide in muscle repair: Nitric oxide-mediated activation of muscle satellite cells. *Mol. Biol. Cell* **11,** 1859–1874.

Apel, E. D., Moscoso, L. M., Glass, D. J., Yancopoulos, G. D., and Sanes, J. R. (1997). Rapsyn is required for MuSK signaling and recruits synaptic components to a MuSK-containing scaffold. *Neuron* **18,** 623–635.

Araishi, K., Sasaoka, T., Imamura, M., Noguchi, S., Hama, H., Wakabayashi, E., Yoshida, M., Hori, T., and Ozawa, E. (1999). Loss of the sarcoglycan complex and sarcospan leads to muscular dystrophy in beta-sarcoglycan-deficient mice. *Hum. Mol. Genet.* **8,** 1589–1598.

Arikawa-Hirasawa, E., Rossi, S. G., Rotundo, R. L., and Yamada, Y. (2002). Absence of acetylcholinesterase at the neuromuscular junctions of perlecan-null mice. *Nat. Neurosci.* **5,** 119–123.

Badorff, C., Lee, G.-H., Lamphear, B. J., Martone, M. E., Campbell, K. P., Rhoads, R. E., and Knowlton, K. U. (1999). Enteroviral protease 2A cleaves dystrophin: Evidence of cytoskeletal disruption in an acquired cardiomyopathy. *Nat. Med.* **5,** 320–326.

Badorff, C., Berkely, N., Mehrotra, S., Talhouk, J. W., Rhoads, R. E., and Knowlton, K. U. (2000). Enteroviral protease 2A directly cleaves dystrophin and is inhibited by a dystrophin-based substrate analogue. *J. Biol. Chem.* **275,** 11191–11197.

Bansal, D., Miyake, K., Vogel, S. S., Groh, S., Chen, C. C., Williamson, R., McNeil, P. L., and Campbell, K. P. (2003). Defective membrane repair in dysferlin-deficient muscular dystrophy. *Nature* **423,** 168–172.

Barresi, R., Michele, D. E., Kanagawa, M., Harper, H..A., Dovico, S. A., Satz, J. S., Moore, S. A., Zhang, W., Schachter, H., Dumanski, J. P., Cohn, R. D., Nishino, I., *et al.* (2004). LARGE can functionally bypass alpha-dystroglycan glycosylation defects in distinct congenital muscular dystrophies. *Nat. Med.* **10,** 696–703.

Bartoli, M., Ramarao, M. K., and Cohen, J. B. (2001). Interactions of the rapsyn RING-H2 domain with dystroglycan. *J. Biol. Chem.* **276,** 24911–24917.

Barton, E. R. (2006). Impact of sarcoglycan complex on mechanical signal transduction in murine skeletal muscle. *Am. J. Physiol. Cell Physiol.* **290,** C411–C419.

Barton, E. R., Morris, L., Musaro, A., Rosenthal, N., and Sweeney, H. L. (2002). Muscle-specific expression of insulin-like growth factor I counters muscle decline in mdx mice. *J. Cell Biol.* **157,** 137–148.

Bassett, D. I., Bryson-Richardson, R. J., Daggett, D. F., Gautier, P., Keenan, D. G., and Currie, P. D. (2003). Dystrophin is required for the formation of stable muscle attachments in the zebrafish embryo. *Development* **130,** 5851–5860.

Batchelor, C. L., and Winder, S. J. (2006). Sparks, signals and shock absorbers: How dystrophin loss causes muscular dystrophy. *Trends Cell Biol.* **16,** 198–205.

Benson, M. A., Newey, S. E., Martin-Rendon, E., Hawkes, R., and Blake, D. J. (2001). Dysbindin, a novel coiled-coil-containing protein that interacts with the dystrobrevins in muscle and brain. *J. Biol. Chem.* **276,** 24232–24241.

Bessou, C., Giugia, J. B., Franks, C. J., Holden-Dye, L., and Segalat, L. (1998). Mutations in the *Caenorhabditis elegans* dystrophin-like gene dys-1 lead to hyperactivity and suggest a link with cholinergic transmission. *Neurogenetics* **2,** 61–72.

Bezakova, G., and Lomo, T. (2001). Muscle activity and muscle agrin regulate the organization of cytoskeletal proteins and attached acetylcholine receptor (AchR) aggregates in skeletal muscle fibers. *J. Cell Biol.* **153,** 1453–1463.

Bhosle, R. C., Michele, D. E., Campbell, K. P., Li, Z., and Robson, R. M. (2006). Interactions of intermediate filament protein synemin with dystrophin and utrophin. *Biochem. Biophys. Res. Commun.* **346,** 768–777.

Blake, D. J., Nawrotzki, R., Peters, M. F., Froehner, S. C., and Davies, K. E. (1996). Isoform diversity of dystrobrevin, the murine 87-kDa postsynaptic protein. *J. Biol. Chem.* **271,** 7802–7810.

Blake, D. J., Nawrotzki, R., Loh, N. Y., Górecki, D. C., and Davies, K. E. (1998). β-Dystrobrevin, a member of the dystrophin-related protein family. *Proc. Natl. Acad. Sci. USA* **95,** 241–246.

Bobet, J., Mooney, R. F., and Gordon, T. (1998). Force and stiffness of old dystrophic (mdx) mouse skeletal muscles. *Muscle Nerve* **21,** 536–539.

Boffi, A., Bozzi, M., Sciandra, F., Woellner, C., Bigotti, M. G., Ilari, A., and Brancaccio, A. (2001). Plasticity of secondary structure in the N-terminal region of beta-dystroglycan. *Biochim. Biophys. Acta* **1546,** 114–121.

Bork, P., and Sudol, M. (1994). The WW domain: A signalling site in dystrophin? *Trends Biochem. Sci.* **19,** 531–533.

Bowe, M. A., Deyst, K. A., Leszyk, J. D., and Fallon, J. R. (1994). Identification and purification of an agrin receptor from Torpedo postsynaptic membranes: A heteromeric complex related to the dystroglycans. *Neuron* **12,** 1173–1180.

Bowe, M. A., Mendis, D. B., and Fallon, J. R. (2000). The small leucine-rich repeat proteoglycan biglycan binds to α-dystroglycan and is upregulated in dystrophic muscle. *J. Cell Biol.* **148,** 801–810.

Bozic, D., Sciandra, F., Lamba, D., and Brancaccio, A. (2004). The structure of the N-terminal region of murine skeletal muscle α-dystroglycan discloses a modular architecture. *J. Biol. Chem.* **279,** 44812–44816.

Brancaccio, A., Schulthess, T., Gesemann, M., and Engel, J. (1995). Electron microscopic evidence for a mucin-like region in chick muscle α-dystroglycan. *FEBS Lett.* **368,** 139–142.

Brancaccio, A., Schulthess, T., Gesemann, M., and Engel, J. (1997). The N-terminal region of α-dystroglycan is an autonomous globular domain. *Eur. J. Biochem.* **246,** 166–172.

Brenman, J. E., Chao, D. S., Xia, H. H., Aldape, K., and Bredt, D. S. (1995). Nitric oxide synthase complexed with dystrophin and absent from skeletal muscle sarcolemma in Duchenne muscular dystrophy. *Cell* **82,** 743–752.

Brooks, S. V. (1998). Rapid recovery following contraction-induced injury to in situ skeletal muscles in *mdx* mice. *J. Muscle Res. Cell Motil.* **19,** 179–187.

Burkin, D. J., Wallace, G. Q., Nicol, K. J., Kaufman, D. J., and Kaufman, S. J. (2001). Enhanced expression of the $\alpha_7\beta_1$ integrin reduces muscular dystrophy and restores viability in dystrophic mice. *J. Cell Biol.* **152,** 1207–1218.

Butler, M. H., Douville, K., Murname, A. A., Kramarcy, N. R., Cohen, J. B., Sealock, R., and Froehner, S. C. (1992). Association of the Mr 58,000 postsynaptic protein of electric tissue with Torpedo dystrophin and the Mr 87,000 postsynaptic protein. *J. Biol. Chem.* **267,** 6213–6218.

Byers, T. J., Kunkel, L. M., and Watkins, S. C. (1991). The subcellular distribution of dystrophin in mouse skeletal, cardiac, and smooth muscle. *J. Cell Biol.* **115,** 411–421.

Campanelli, J. T., Roberds, S. L., Campbell, K. P., and Scheller, R. H. (1994). A role for dystrophin-associated glycoproteins and utrophin in agrin-induced AChR clustering. *Cell* **77,** 663–674.

Carlson, C. G., and Makiejus, R. V. (1990). A noninvasive procedure to detect muscle weakness in the *mdx* mouse. *Muscle Nerve* **13,** 480–484.

Cartaud, A., Coutant, S., Petrucci, T. C., and Cartaud, J. (1998). Evidence for *in situ* and *in vitro* association between β-dystroglycan and the subsynaptic 43K rapsyn protein—Consequence for acetylcholine receptor clustering at the synapse. *J. Biol. Chem.* **273,** 11321–11326.

Chen, Y.-W., Zhao, P., Borup, R., and Hoffman, E. P. (2000). Expression profiling in the muscular dystrophies: Identification of novel aspects of molecular pathophysiology. *J. Cell Biol.* **151,** 1321–1336.

Chung, W., and Campanelli, J. T. (1999). WW and EF hand domains of dystrophin-family proteins mediate dystroglycan binding. *Mol. Cell. Biol. Res. Commun.* **2,** 162–171.

Clarke, M. S. F., Khakee, R., and McNeil, P. L. (1993). Loss of cytoplasmic basic fibroblast growth factor from physiologically wounded myofibers of normal and dystrophic muscle. *J. Cell Sci.* **106,** 121–133.

Cohn, R., Henry, M., Michele, D., Barresi, R., Saito, F., Moore, S., Flanagan, J., Skwarchuk, M., Robbins, M., Mendell, J., Williamson, R., and Campbell, K. (2002). Disruption of dag1 in differentiated skeletal muscle reveals a role for dystroglycan in muscle regeneration. *Cell* **110,** 639.

Connolly, A. M., Keeling, R. M., Mehta, S., Pestronk, A., and Sanes, J. R. (2001). Three mouse models of muscular dystrophy: The natural history of strength and fatigue in dystrophin-, dystrophin/utrophin-, and laminin α2-deficient mice. *Neuromuscul. Disord.* **11,** 703–712.

Coral-Vazquez, R., Cohn, R. D., Moore, S. A., Hill, J. A., Weiss, R. M., Davisson, R. L., Straub, V., Barresi, R., Bansal, D., Hrstka, R. F., Williamson, R., and Campbell, K. P. (1999). Disruption of the sarcoglycan-sarcospan complex in vascular smooth muscle: A novel mechanism for cardiomyopathy and muscular dystrophy. *Cell* **98,** 465–474.

Corrado, K., Mills, P. L., and Chamberlain, J. S. (1994). Deletion analysis of the dystrophin-actin binding domain. *FEBS Lett.* **344,** 255–260.

Cote, P. D., Moukhles, H., Lindenbaum, M., and Carbonetto, S. (1999). Chimaeric mice deficient in dystroglycans develop muscular dystrophy and have disrupted myoneural synapses. *Nat. Genet.* **23,** 338–342.

Coulton, G. R., Curtin, N. A., Morgan, J. E., and Partridge, T. A. (1988). The *mdx* mouse skeletal muscle myopathy: II. Contractile properties. *Neuropathol. Appl. Neurobiol.* **14,** 299–314.

Cox, G. A., Cole, N. M., Matsumura, K., Phelps, S. F., Hauschka, S. D., Campbell, K. P., Faulkner, J. A., and Chamberlain, J. S. (1993). Overexpression of dystrophin in transgenic *mdx* mice eliminates dystrophic symptoms without toxicity. *Nature* **364,** 725–729.

Cox, G. A., Sunada, Y., Campbell, K. P., and Chamberlain, J. S. (1994). Dp71 can restore the dystrophin-associated glycoprotein complex in muscle but fails to prevent dystrophy. *Nat. Genet.* **8,** 333–339.

Craig, S. W., and Pardo, J. V. (1983). Gamma actin, spectrin, and intermediate filament proteins colocalize with vinculin at costameres, myofibril-to-sarcolemma attachment sites. *Cell Motil.* **3,** 449–462.

Crosbie, R. H., Heighway, J., Venzke, D. P., Lee, J. C., and Campbell, K. P. (1997). Sarcospan, the 25-kDa transmembrane component of the dystrophin-glycoprotein complex. *J. Biol. Chem.* **272,** 31221–31224.

Crosbie, R. H., Lebakken, C. S., Holt, K. H., Venzke, D. P., Straub, V., Lee, J. C., Grady, R. M., Chamberlain, J. S., Sanes, J. R., and Campbell, K. P. (1999). Membrane

targeting and stabilization of sarcospan is mediated by the sarcoglycan subcomplex. *J. Cell Biol.* **145,** 153–165.

Dalkilic, I., Schienda, J., Thompson, T. G., and Kunkel, L. M. (2006). Loss of filaminC (FLNc) results in severe defects in myogenesis and myotube structure. *Mol. Cell. Biol.* **26,** 6522–6534.

Danialou, G., Comtois, A. S., Dudley, R., Karpati, G., Vincent, G., Des Rosiers, C., and Petrof, B. J. (2001). Dystrophin-deficient cardiomyocytes are abnormally vulnerable to mechanical stress-induced contractile failure and injury. *FASEB J.* **15,** 1655–1658.

Danowski, B. A., Imanaka-Yoshida, K., Sanger, J. M., and Sanger, J. W. (1992). Costameres are sites of force transmission to the substratum in adult rat cardiomyocytes. *J. Cell Biol.* **118,** 1411–1420.

Deconinck, N., Ragot, T., Maréchal, G., Perricaudet, M., and Gillis, J. M. (1996). Functional protection of dystrophic mouse (*mdx*) muscles after adenovirus-mediated transfer of a dystrophin minigene. *Proc. Natl. Acad. Sci. USA* **93,** 3570–3574.

Deconinck, A. E., Potter, A. C., Tinsley, J. M., Wood, S. J., Vater, R., Young, C., Metzinger, L., Vincent, A., Slater, C. R., and Davies, K. E. (1997a). Postsynaptic abnormalities at the neuromuscular junctions of utrophin-deficient mice. *J. Cell Biol.* **136,** 883–894.

Deconinck, A. E., Rafael, J. A., Skinner, J. A., Brown, S. C., Potter, A. C., Metzinger, L., Watt, D. J., Dickson, J. G., Tinsley, J. M., and Davies, K. E. (1997b). Utrophin-dystrophin-deficient mice as a model for Duchenne muscular dystrophy. *Cell* **90,** 717–727.

Deconinck, N., Tinsley, J., De Backer, F., Fisher, R., Kahn, D., Phelps, S., Davies, K., and Gillis, J. M. (1997c). Expression of truncated utrophin leads to major functional improvements in dystrophin-deficient muscles of mice. *Nat. Med.* **3,** 1216–1221.

Deconinck, N., Rafael, J. A., Beckers-Bleukx, G., Kahn, D., Deconinck, A., Davies, K. E., and Gillis, J. M. (1998). Consequences of the combined deficiency in dystrophin and utrophin on the mechanical properties and myosin composition of some limb and respiratory muscles of the mouse. *Neuromuscul. Disord.* **8,** 362–370.

DelloRusso, C., Crawford, R. W., Chamberlain, J. S., and Brooks, S. V. (2001). Tibialis anterior muscles in *mdx* mice are highly susceptible to contraction-induced injury. *J. Muscle Res. Cell Motil.* **22,** 467–475.

DeWolf, C., McCauley, P., Sikorski, A. F., Winlove, C. P., Bailey, A. I., Kahana, E., Pinder, J. C., and Gratzer, W. B. (1997). Interaction of dystrophin fragments with model membranes. *Biophys. J.* **72,** 2599–2604.

Deyst, K. A., Bowe, M. A., Leszyk, J. D., and Fallon, J. R. (1995). The α-dystroglycan-β-dystroglycan complex—Membrane organization and relationship to an agrin receptor. *J. Biol. Chem.* **270,** 25956–25959.

Di, S. E., Sciandra, F., Maras, B., Di, T. F., Petrucci, T. C., Giardina, B., and Brancaccio, A. (1999). Structural and functional analysis of the N-terminal extracellular region of β-dystroglycan. *Biochem. Biophys. Res. Commun.* **266,** 274–278.

Dogra, C., Changotra, H., Wergedal, J. E., and Kumar, A. (2006). Regulation of phosphatidylinositol 3-kinase (PI3K)/Akt and nuclear factor-kappa B signaling pathways in dystrophin-deficient skeletal muscle in response to mechanical stretch. *J. Cell Physiol.* **208,** 575–585.

Dominov, J. A., Kravetz, A. J., Ardelt, M., Kostek, C. A., Beermann, M. L., and Miller, J. B. (2005). Muscle-specific BCL2 expression ameliorates muscle disease in laminin α2-deficient, but not in dystrophin-deficient, mice. *Hum. Mol. Genet.* **14,** 1029–1040.

Duclos, F., Straub, V., Moore, S. A., Venzke, D. P., Hrstka, R. F., Crosbie, R. H., Durbeej, M., Lebakken, C. S., Ettinger, A. J., Van der Meulen, J., Holt, K. H., Lim, L. E., *et al.* (1998). Progressive muscular dystrophy in α-sarcoglycan-deficient mice. *J. Cell Biol.* **142,** 1461–1471.

Dudley, R. W., Danialou, G., Govindaraju, K., Lands, L., Eidelman, D. E., and Petrof, B. J. (2006). Sarcolemmal damage in dystrophin deficiency is modulated by synergistic interactions between mechanical and oxidative/nitrosative stresses. *Am. J. Pathol.* **168,** 1276–1287.

Durbeej, M., Cohn, R. D., Hrstka, R. F., Moore, S. A., Allamand, V., Davidson, B. L., Williamson, R. A., and Campbell, K. P. (2000). Disruption of the β-sarcoglycan gene reveals pathogenetic complexity of limb-girdle muscular dystrophy type 2E. *Mol. Cell* **5,** 141–151.

Dwyer, T..M., and Froehner, S. C. (1995). Direct binding of *Torpedo* syntrophin to dystrophin and the 87 kDa dystrophin homologue. *Febs Lett.* **375,** 91–94.

Ehmer, S., Herrmann, R., Bittner, R., and Voit, T. (1997). Spatial distribution of β-spectrin in normal and dystrophic human skeletal muscle. *Acta Neuropathol. (Berl.)* **94,** 240–246.

Engel, A. G. (1986). Duchenne Dystrophy. *In* "Myology: Basic and Clinical" (A. G. Engel and B. Q. Banker, eds.), pp. 1185–1240. McGraw-Hill, New York.

Ervasti, J. M., and Campbell, K. P. (1991). Membrane organization of the dystrophin–glycoprotein complex. *Cell* **66,** 1121–1131.

Ervasti, J. M., and Campbell, K. P. (1993). A role for the dystrophin–glycoprotein complex as a transmembrane linker between laminin and actin. *J. Cell Biol.* **122,** 809–823.

Ervasti, J. M., Ohlendieck, K., Kahl, S. D., Gaver, M. G., and Campbell, K. P. (1990). Deficiency of a glycoprotein component of the dystrophin complex in dystrophic muscle. *Nature* **345,** 315–319.

Ervasti, J. M., Kahl, S. D., and Campbell, K. P. (1991). Purification of dystrophin from skeletal muscle. *J. Biol. Chem.* **266,** 9161–9165.

Ervasti, J. M., Burwell, A. L., and Geissler, A. L. (1997). Tissue-specific heterogeneity in α-dystroglycan sialoglycosylation: Skeletal muscle α-dystroglycan is a latent receptor for *Vicia villosa* agglutinin B_4 masked by sialic acid modification. *J. Biol. Chem.* **272,** 22315–22321.

Esapa, C. T., Bentham, G. R., Schroder, J. E., Kroger, S., and Blake, D. J. (2003). The effects of post-translational processing on dystroglycan synthesis and trafficking. *FEBS Lett.* **555,** 209–216.

Etard, C., Behra, M., Ertzer, R., Fischer, N., Jesuthasan, S., Blader, P., Geisler, R., and Strahle, U. (2005). Mutation in the δ-subunit of the nAChR suppresses the muscle defects caused by lack of dystrophin. *Dev. Dyn.* **234,** 1016–1025.

Ettinger, A. J., Feng, G., and Sanes, J. R. (1997). ϵ-Sarcoglycan, a broadly expressed homologue of the gene mutated in limb-girdle muscular dystrophy. *J. Biol. Chem.* **272,** 32534–32538.

Fabbrizio, E., Bonet-Kerrache, A., Leger, J. J., and Mornet, D. (1993). Actin-dystrophin interface. *Biochemistry* **32,** 10457–10463.

Gautam, M., Noakes, P. G., Moscoso, L., Rupp, F., Scheller, R. H., Merlie, J. P., and Sanes, J. R. (1996). Defective neuromuscular synaptogenesis in agrin-deficient mutant mice. *Cell* **85,** 525–535.

Gee, S. H., Blacher, R. W., Douville, P. J., Provost, P. R., Yurchenco, P. D., and Carbonetto, S. (1993). Laminin-binding protein 120 from brain is closely related to the dystrophin-associated glycoprotein, dystroglycan, and binds with high affinity to the major heparin binding domain of laminin. *J. Biol. Chem.* **268,** 14972–14980.

Gee, S. H., Montanaro, F., Lindenbaum, M. H., and Carbonetto, S. (1994). Dystroglycan-α, a dystrophin-associated glycoprotein, is a functional agrin receptor. *Cell* **77,** 675–686.

Gee, S. H., Madhavan, R., Levinson, S. R., Caldwell, J. H., Sealock, R., and Froehner, S. C. (1998). Interaction of muscle and brain sodium channels with multiple members of the syntrophin family of dystrophin-associated proteins. *J. Neurosci.* **18,** 128–137.

Gieseler, K., Bessou, C., and Segalat, L. (1999). Dystrobrevin- and dystrophin-like mutants display similar phenotypes in the nematode *Caenorhabditis elegans*. *Neurogenetics* **2,** 87–90.

Gieseler, K., Grisoni, K., and Segalat, L. (2000). Genetic suppression of phenotypes arising from mutations in dystrophin-related genes in *Caenorhabditis elegans*. *Curr. Biol.* **10,** 1092–1097.

Gieseler, K., Mariol, M. C., Bessou, C., Migaud, M., Franks, C. J., Holden-Dye, L., and Segalat, L. (2001). Molecular, genetic and physiological characterisation of dystrobrevin-like (dyb-1) mutants of *Caenorhabditis elegans*. *J. Mol. Biol.* **307,** 107–117.

Girgenrath, M., Dominov, J. A., Kostek, C. A., and Miller, J. B. (2004). Inhibition of apoptosis improves outcome in a model of congenital muscular dystrophy. *J. Clin. Invest.* **114,** 1635–1639.

Grady, R. M., Merlie, J. P., and Sanes, J. R. (1997a). Subtle neuromuscular defects in utrophin-deficient mice. *J. Cell Biol.* **136,** 871–882.

Grady, R. M., Teng, H. B., Nichol, M. C., Cunningham, J. C., Wilkinson, R. S., and Sanes, J. R. (1997b). Skeletal and cardiac myopathies in mice lacking utrophin and dystrophin: A model for Duchenne muscular dystrophy. *Cell* **90,** 729–738.

Grady, R. M., Grange, R. W., Lau, K. S., Maimone, M. M., Nichol, M. C., Stull, J. T., and Sanes, J. R. (1999). Role for α-dystrobrevin in the pathogenesis of dystrophin-dependent muscular dystrophies. *Nat. Cell Biol.* **1,** 215–220.

Grady, R. M., Zhou, H., Cunningham, J. M., Henry, M. D., Campbell, K. P., and Sanes, J. R. (2000). Maturation and maintenance of the neuromuscular synapse: Genetic evidence for roles of the dystrophin–glycoprotein complex. *Neuron* **25,** 279–293.

Grady, R. M., Akaaboune, M., Cohen, A. L., Maimone, M. M., Lichtman, J. W., and Sanes, J. R. (2003). Tyrosine-phosphorylated and nonphosphorylated isoforms of α-dystrobrevin: Roles in skeletal muscle and its neuromuscular and myotendinous junctions. *J. Cell Biol.* **160,** 741–752.

Greenberg, D. S., Sunada, Y., Campbell, K. P., Yaffe, D., and Nudel, U. (1994). Exogenous Dp71 restores the levels of dystrophin associated proteins but does not alleviate muscle damage in *mdx* mice. *Nat. Genet.* **8,** 340–344.

Greener, M. J., and Roberts, R. G. (2000). Conservation of components of the dystrophin complex in *Drosophila*. *FEBS Lett.* **482,** 13–18.

Grewal, P. K., Holzfeind, P. J., Bittner, R. E., and Hewitt, J. E. (2001). Mutant glycosyltransferase and altered glycosylation of α-dystroglycan in the myodystrophy mouse. *Nat. Genet.* **28,** 151–154.

Griffin, M. A., Feng, H., Tewari, M., Acosta, P., Kawana, M., Sweeney, H. L., and Discher, D. E. (2005). γ-Sarcoglycan deficiency increases cell contractility, apoptosis and MAPK pathway activation but does not affect adhesion. *J. Cell Sci.* **118,** 1405–1416.

Grisoni, K., Martin, E., Gieseler, K., Mariol, M. C., and Segalat, L. (2002). Genetic evidence for a dystrophin–glycoprotein complex (DGC) in *Caenorhabditis elegans*. *Gene* **294,** 77–86.

Grisoni, K., Gieseler, K., Mariol, M. C., Martin, E., Carre-Pierrat, M., Moulder, G., Barstead, R., and Segalat, L. (2003). The stn-1 syntrophin gene of *C. elegans* is functionally related to dystrophin and dystrobrevin. *J. Mol. Biol.* **332,** 1037–1046.

Guyon, J. R., Mosley, A. N., Zhou, Y., O'Brien, K. F., Sheng, X., Chiang, K., Davidson, A. J., Volinski, J. M., Zon, L. I., and Kunkel, L. M. (2003). The dystrophin associated protein complex in zebrafish. *Hum. Mol. Genet.* **12,** 601–615.

Hack, A. A., Ly, C. T., Jiang, F., Clendenin, C. J., Sigrist, K. S., Wollmann, R. L., and McNally, E. M. (1998). γ-Sarcoglycan deficiency leads to muscle membrane defects and apoptosis independent of dystrophin. *J. Cell Biol.* **142,** 1279–1287.

Hack, A. A., Lam, M. Y., Cordier, L., Shoturma, D. I., Ly, C. T., Hadhazy, M. A., Hadhazy, M. R., Sweeney, H. L., and McNally, E. M. (2000). Differential requirement

for individual sarcoglycans and dystrophin in the assembly and function of the dystrophin–glycoprotein complex. *J. Cell Sci.* **113(Pt. 14),** 2535–2544.

Hall, T. E., Bryson-Richardson, R. J., Berger, S., Jacoby, A. S., Cole, N. J., Hollway, G. E., Berger, J., and Currie, P. D. (2007). The zebrafish candyfloss mutant implicates extracellular matrix adhesion failure in laminin α2-deficient congenital muscular dystrophy. *Proc. Natl. Acad. Sci. USA* **104,** 7092–7097.

Hanft, L. M., Rybakova, I. N., Patel, J. R., Rafael-Fortney, J. A., and Ervasti, J. M. (2006). Cytoplasmic γ-actin contributes to a compensatory remodeling response in dystrophin-deficient muscle. *Proc. Natl. Acad. Sci. USA* **103,** 5385–5390.

Harper, S. Q., Hauser, M. A., DelloRusso, C., Duan, D., Crawford, R. W., Phelps, S. F., Harper, H. A., Robinson, A. S., Engelhardt, J. F., Brooks, S. V., and Chamberlain, J. S. (2002). Modular flexibility of dystrophin: Implications for gene therapy of Duchenne muscular dystrophy. *Nat. Med.* **8,** 253–261.

Helbling-Leclerc, A., Zhang, X., Topaloglu, H., Cruaud, C., Tesson, F., Weissenbach, J., Tomé, F. M. S., Schwartz, K., Fardeau, M., Tryggvason, K., and Guicheney, P. (1995). Mutations in the laminin α2-chain gene (*LAMA2)* cause merosin-deficient congenital muscular dystrophy. *Nat. Genet.* **11,** 216–218.

Hemmings, L., Kuhlman, P. A., and Critchley, D. R. (1992). Analysis of the actin-binding domain of α-actinin by mutagenesis and demonstration that dystrophin contains a functionally homologous domain. *J. Cell Biol.* **116,** 1369–1380.

Hodges, B. L., Hayashi, Y. K., Nonaka, I., Wang, W., Arahata, K., and Kaufman, S. J. (1997). Altered expression of the α7β1 integrin in human and murine muscular dystrophies. *J. Cell Sci.* **110,** 2873–2881.

Hoffman, E. P., Brown, R. H., and Kunkel, L. M. (1987). Dystrophin: The protein product of the Duchenne muscular dystrophy locus. *Cell* **51,** 919–928.

Hohenester, E., Tisi, D., Talts, J. F., and Timpl, R. (1999). The crystal structure of a laminin G-like module reveals the molecular basis of α-dystroglycan binding to laminins, perlecan, and agrin. *Mol. Cell* **4,** 783–792.

Holt, K. H., Crosbie, R. H., Venzke, D. P., and Campbell, K. P. (2000). Biosynthesis of dystroglycan: Processing of a precursor propeptide. *FEBS Lett.* **468,** 79–83.

Holzfeind, P. J., Ambrose, H. J., Newey, S. E., Nawrotzki, R. A., Blake, D. J., and Davies, K. E. (1999). Tissue-selective expression of α-dystrobrevin is determined by multiple promoters. *J. Biol. Chem.* **274,** 6250–6258.

Hosaka, Y., Yokota, T., Miyagoe-Suzuki, Y., Yuasa, K., Imamura, M., Matsuda, R., Ikemoto, T., Kameya, S., and Takeda, S. (2002). α1-Syntrophin-deficient skeletal muscle exhibits hypertrophy and aberrant formation of neuromuscular junctions during regeneration. *J. Cell Biol.* **158,** 1097–1107.

Hoyte, K., Jayasinha, V., Xia, B., and Martin, P. T. (2004). Transgenic overexpression of dystroglycan does not inhibit muscular dystrophy in *mdx* mice. *Am. J. Pathol.* **164,** 711–718.

Huang, P. L., Dawson, T. M., Bredt, D. S., Snyder, S. H., and Fishman, M. C. (1993). Targeted disruption of the neuronal nitric oxide synthase gene. *Cell* **75,** 1273–1286.

Huang, X., Poy, F., Zhang, R., Joachimiak, A., Sudol, M., and Eck, M. J. (2000). Structure of a WW domain containing fragment of dystrophin in complex with β-dystroglycan. *Nat. Struct. Biol.* **7,** 634–638.

Ibraghimov-Beskrovnaya, O., Ervasti, J. M., Leveille, C. J., Slaughter, C. A., Sernett, S. W., and Campbell, K. P. (1992). Primary structure of dystrophin-associated glycoproteins linking dystrophin to the extracellular matrix. *Nature* **355,** 696–702.

Imamura, M., Mochizuki, Y., Engvall, E., and Takeda, S. (2005). Epsilon-sarcoglycan compensates for lack of α-sarcoglycan in a mouse model of limb-girdle muscular dystrophy. *Hum. Mol. Genet.* **14,** 775–783.

Ishikawa-Sakurai, M., Yoshida, M., Imamura, M., Davies, K. E., and Ozawa, E. (2004). ZZ domain is essentially required for the physiological binding of dystrophin and utrophin to β-dystroglycan. *Hum. Mol. Genet.* **13,** 693–702.

Iwata, Y., Pan, Y., Yoshida, T., Hanada, H., and Shigekawa, M. (1998). α1-Syntrophin has distinct binding sites for actin and calmodulin. *FEBS Lett.* **423,** 173–177.

Iwata, Y., Sampaolesi, M., Shigekawa, M., and Wakabayashi, S. (2004). Syntrophin is an actin-binding protein the cellular localization of which is regulated through cytoskeletal reorganization in skeletal muscle cells. *Eur. J. Cell Biol.* **83,** 555–565.

Jarrett, H. W., and Foster, J. L. (1995). Alternate binding of actin and calmodulin to multiple sites on dystrophin. *J. Biol. Chem.* **270,** 5578–5586.

Jayasinha, V., Nguyen, H. H., Xia, B., Kammesheidt, A., Hoyte, K., and Martin, P. T. (2003). Inhibition of dystroglycan cleavage causes muscular dystrophy in transgenic mice. *Neuromuscul. Disord.* **13,** 365–375.

Jin, H., Tan, S., Hermanowski, J., Bohm, S., Pacheco, S., McCauley, J. M., Greener, M. J., Hinits, Y., Hughes, S. M., Sharpe, P. T., and Roberts, R. G. (2007). The dystrotelin, dystrophin and dystrobrevin superfamily: New paralogues and old isoforms. *BMC Genomics* **8,** 19.

Judge, L. M., Haraguchiln, M., and Chamberlain, J. S. (2006). Dissecting the signaling and mechanical functions of the dystrophin–glycoprotein complex. *J. Cell Sci.* **119,** 1537–1546.

Jung, D., Yang, B., Meyer, J., Chamberlain, J. S., and Campbell, K. P. (1995). Identification and characterization of the dystrophin anchoring site on β-dystroglycan. *J. Biol. Chem.* **270,** 27305–27310.

Kameya, S., Miyagoe, Y., Nonaka, I., Ikemoto, T., Endo, M., Hanaoka, K., Nabeshima, Y., and Takeda, S. (1999). α1-Syntrophin gene disruption results in the absence of neuronal-type nitric-oxide synthase at the sarcolemma but does not induce muscle degeneration. *J. Biol. Chem.* **274,** 2193–2200.

Kamogawa, Y., Biro, S., Maeda, M., Setoguchi, M., Hirakawa, T., Yoshida, H., and Tei, C. (2001). Dystrophin-deficient myocardium is vulnerable to pressure overload *in vivo*. *Cardiovasc. Res.* **50,** 509–515.

Kanagawa, M., Saito, F., Kunz, S., Yoshida-Moriguchi, T., Barresi, R., Kobayashi, Y. M., Muschler, J., Dumanski, J. P., Michele, D. E., Oldstone, M. B., and Campbell, K. P. (2004). Molecular recognition by LARGE is essential for expression of functional dystroglycan. *Cell* **117,** 953–964.

Kanagawa, M., Michele, D. E., Satz, J. S., Barresi, R., Kusano, H., Sasaki, T., Timpl, R., Henry, M. D., and Campbell, K. P. (2005). Disruption of perlecan binding and matrix assembly by post-translational or genetic disruption of dystroglycan function. *FEBS Lett.* **579,** 4792–4796.

Kaprielian, R. R., Stevenson, S., Rothery, S. M., Cullen, M. J., and Severs, N. J. (2000). Distinct patterns of dystrophin organization in myocyte sarcolemma and transverse tubules of normal and diseased human myocardium. *Circulation* **101,** 2586–2594.

Karpati, G., and Carpenter, S. (1986). Small-caliber skeletal muscle fibers do not suffer deleterious consequences of dystrophic gene expression. *Am. J. Med. Genet.* **25,** 653–658.

Khurana, T. S., Watkins, S. C., Chafey, P., Chelly, J., Tome, F. M. S., Fardeau, M., Kaplan, J. C., and Kunkel, L. M. (1991). Immunolocalization and developmental expression of dystrophin related protein in skeletal muscle. *Neuromuscul. Disord.* **1,** 185–194.

Kim, H., Rogers, M. J., Richmond, J. E., and McIntire, S. L. (2004). SNF-6 is an acetylcholine transporter interacting with the dystrophin complex in *Caenorhabditis elegans*. *Nature* **430,** 891–896.

Koenig, M., and Kunkel, L. M. (1990). Detailed analysis of the repeat domain of dystrophin reveals four potential hinge segments that may confer flexibility. *J. Biol. Chem.* **265,** 4560–4566.

Koenig, M., Monaco, A. P., and Kunkel, L. M. (1988). The complete sequence of dystrophin predicts a rod-shaped cytoskeletal protein. *Cell* **53,** 219–228.

Kolodziejczyk, S. M., Walsh, G. S., Balazsi, K., Seale, P., Sandoz, J., Hierlihy, A. M., Rudnicki, M. A., Chamberlain, J. S., Miller, F. D., and Megeney, L. A. (2001). Activation of JNK1 contributes to dystrophic muscle pathogenesis. *Curr. Biol.* **11,** 1278–1282.

Kometani, K., Tsugeno, H., and Yamada, K. (1990). Mechanical and energetic properties of dystrophic (mdx) mouse muscle. *Jpn. J. Physiol.* **40,** 541–549.

Kramarcy, N. R., Vidal, A., Froehner, S. C., and Sealock, R. (1994). Association of utrophin and multiple dystrophin short forms with the mammalian M_r 58,000 dystrophin-associated protein (syntrophin). *J. Biol. Chem.* **269,** 2870–2876.

Kumar, A., Khandelwal, N., Malya, R., Reid, M. B., and Boriek, A. M. (2004). Loss of dystrophin causes aberrant mechanotransduction in skeletal muscle fibers. *FASEB J.* **18,** 102–113.

Kunz, S., Calder, L., and Oldstone, M. B. (2004). Electron microscopy of an alpha-dystroglycan fragment containing receptor sites for lymphocytic choriomeningitis virus and laminin, and use of the receptoid body as a reagent to neutralize virus. *Virology* **325,** 207–215.

Lang, J. M., Esser, K. A., and Dupont-Versteegden, E. E. (2004). Altered activity of signaling pathways in diaphragm and tibialis anterior muscle of dystrophic mice. *Exp. Biol. Med. (Maywood)* **229,** 503–511.

Langenbach, K. J., and Rando, T. A. (2002). Inhibition of dystroglycan binding to laminin disrupts the PI3K/AKT pathway and survival signaling in muscle cells. *Muscle Nerve* **26,** 644–653.

Law, D. J., and Tidball, J. G. (1993). Dystrophin deficiency is associated with myotendinous junction defects in prenecrotic and fully regenerated skeletal muscle. *Am. J. Pathol.* **142,** 1513–1523.

Law, D. J., Allen, D. L., and Tidball, J. G. (1994). Talin, vinculin and DRP (utrophin) concentrations are increased at *mdx* myotendinous junctions following onset of necrosis. *J. Cell Sci.* **107,** 1477–1483.

Le, R. E., Fichou, Y., Pottier, S., Gaboriau, F., Rondeau-Mouro, C., Vincent, M., Gallay, J., and Bondon, A. (2003). Interaction of dystrophin rod domain with membrane phospholipids. Evidence of a close proximity between tryptophan residues and lipids. *J. Biol. Chem.* **278,** 5993–6001.

Lebakken, C. S., Venzke, D. P., Hrstka, R. F., Consolino, C. M., Faulkner, J. A., Williamson, R. A., and Campbell, K. P. (2000). Sarcospan-deficient mice maintain normal muscle function. *Mol. Cell. Biol.* **20,** 1669–1677.

Lebart, M. C., Casanova, D., and Benyamin, Y. (1995). Actin interaction with purified dystrophin from electric organ of *Torpedo marmorata*: Possible resemblance with filamin actin interface. *J. Muscle Res. Cell Motil.* **16,** 543–552.

Lefebvre, J. L., Jing, L., Becaficco, S., Franzini-Armstrong, C., and Granato, M. (2007). Differential requirement for MuSK and dystroglycan in generating patterns of neuromuscular innervation. *Proc. Natl. Acad. Sci. USA* **104,** 2483–2488.

Lim, L. E., Duclos, F., Broux, O., Bourg, N., Sunada, Y., Allamand, V., Meyer, J., Richard, I. Z., Moomaw, C., Slaughter, C., Tomé, F. M. S., Fardeau, M., *et al.* (1995). *β*-Sarcoglycan: Characterization and role in limb-girdle muscular dystrophy linked to 4q12. *Nat. Genet.* **11,** 257–265.

Lowe, D. A., Williams, B. O., Thomas, D. D., and Grange, R. W. (2006). Molecular and cellular contractile dysfunction of dystrophic muscle from young mice. *Muscle Nerve* **34,** 92–100.

Lumeng, C., Phelps, S., Crawford, G. E., Walden, P. D., Barald, K., and Chamberlain, J. S. (1999). Interactions between beta 2-syntrophin and a family of microtubule-associated serine/threonine kinases. *Nat. Neurosci.* **2,** 611–617.

Luo, S., Chen, Y., Lai, K. O., Arevalo, J. C., Froehner, S. C., Adams, M. E., Chao, M. V., and Ip, N. Y. (2005). α-Syntrophin regulates ARMS localization at the neuromuscular junction and enhances EphA4 signaling in an ARMS-dependent manner. *J. Cell Biol.* **169,** 813–824.

Lynch, G. S., Rafael, J. A., Chamberlain, J. S., and Faulkner, J. A. (2000). Contraction-induced injury to single permeabilized muscle fibers from *mdx*, transgenic mdx, and control mice. *Am. J. Physiol. Cell Physiol.* **279,** C1290–C1294.

Lynch, G. S., Hinkle, R. T., Chamberlain, J. S., Brooks, S. V., and Faulkner, J. A. (2001). Force and power output of fast and slow skeletal muscles from *mdx* mice 6–28 months old. *J. Physiol.* **535,** 591–600.

Lyons, P. R., and Slater, C. R. (1991). Structure and function of the neuromuscular junction in young adult *mdx* mice. *J. Neurocytol.* **20,** 969–981.

Mariol, M. C., Martin, E., Chambonnier, L., and Segalat, L. (2007). Dystrophin-dependent muscle degeneration requires a fully functional contractile machinery to occur in *C. elegans*. *Neuromuscul. Disord.* **17,** 56–60.

Matsuda, R., Nishikawa, A., and Tanaka, H. (1995). Visualization of dystrophic muscle fibers in *mdx* mouse by vital staining with Evans Blue: Evidence of apoptosis in dystrophin-deficient muscle. *J. Biochem. (Tokyo)* **118,** 959–964.

Matsumura, K., Ervasti, J. M., Ohlendieck, K., Kahl, S. D., and Campbell, K. P. (1992). Association of dystrophin-related protein with dystrophin-associated proteins in *mdx* mouse muscle. *Nature* **360,** 588–591.

McNally, E. M., Ly, C. T., and Kunkel, L. M. (1998). Human ϵ-sarcoglycan is highly related to α-sarcoglycan (adhalin), the limb girdle muscular dystrophy 2D gene. *FEBS Lett.* **422,** 27–32.

Megeney, L. A., Kablar, B., Perry, R. L. S., Ying, C. Y., May, L., and Rudnicki, M. A. (1999). Severe cardiomyopathy in mice lacking dystrophin and MyoD. *Proc. Natl. Acad. Sci. USA* **96,** 220–225.

Meinen, S., Barzaghi, P., Lin, S., Lochmuller, H., and Ruegg, M. A. (2007). Linker molecules between laminins and dystroglycan ameliorate laminin-α2-deficient muscular dystrophy at all disease stages. *J. Cell Biol.* **176,** 979–993.

Menke, A., and Jockusch, H. (1991). Decreased osmotic stability of dystrophin-less muscle cells from the *mdx* mouse. *Nature* **349,** 69–71.

Menke, A., and Jockusch, H. (1995). Extent of shock-induced membrane leakage in human and mouse myotubes depends on dystrophin. *J. Cell Sci.* **108,** 727–733.

Mercado, M. L., Amenta, A. R., Hagiwara, H., Rafii, M. S., Lechner, B. E., Owens, R. T., McQuillan, D. J., Froehner, S. C., and Fallon, J. R. (2006). Biglycan regulates the expression and sarcolemmal localization of dystrobrevin, syntrophin, and nNOS. *FASEB J.* **20,** 1724–1726.

Michele, D. E., Barresi, R., Kanagawa, M., Saito, F., Cohn, R. D., Satz, J. S., Dollar, J., Nishino, I., Kelley, R. I., Somer, H., Straub, V., Mathews, K. D., *et al.* (2002). Post-translational disruption of dystroglycan-ligand interactions in congenital muscular dystrophies. *Nature* **418,** 417–422.

Minetti, C., Tanji, K., and Bonilla, E. (1992). Immunologic study of vinculin in Duchenne muscular dystrophy. *Neurology* **42,** 1751–1754.

Minetti, C., Tanji, K., Rippa, P. G., Morreale, G., Cordone, G., and Bonilla, E. (1994). Abnormalities in the expression of β-spectrin in Duchenne muscular dystrophy. *Neurology* **44,** 1149–1153.

Mizuno, Y. (1992). Prevention of myonecrosis in mdx mice: Effect of immobilization by the local tetanus method. *Brain Dev* **14,** 319–322.

Mizuno, Y., Thompson, T. G., Guyon, J. R., Lidov, H. G., Brosius, M., Imamura, M., Ozawa, E., Watkins, S. C., and Kunkel, L. M. (2001). Desmuslin, an intermediate filament protein that interacts with α-dystrobrevin and desmin. *Proc. Natl. Acad. Sci. USA* **98,** 6156–6161.

Moens, P., Baatsen, P. H., and Marechal, G. (1993). Increased susceptibility of EDL muscles from *mdx* mice to damage induced by contractions with stretch. *J. Muscle Res. Cell Motil.* **14,** 446–451.

Mokhtarian, A., Lefaucheur, J. P., Even, P. C., and Sebille, A. (1999). Hindlimb immobilization applied to 21-day-old *mdx* mice prevents the occurrence of muscle degeneration. *J. Appl. Physiol.* **86,** 924–931.

Mokri, B., and Engel, A. G. (1975). Duchenne dystrophy: Electron microscopic findings pointing to a basic or early abnormality in the plasma membrane of the muscle fiber. *Neurology* **25,** 1111–1120.

Moll, J., Barzaghi, P., Lin, S., Bezakova, G., Lochmuller, H., Engvall, E., Muller, U., and Ruegg, M. A. (2001). An agrin minigene rescues dystrophic symptoms in a mouse model for congenital muscular dystrophy. *Nature* **413,** 302–307.

Montana, E. S., and Littleton, J. T. (2004). Characterization of a hypercontraction-induced myopathy in *Drosophila* caused by mutations in Mhc. *J. Cell Biol.* **164,** 1045–1054.

Montana, E. S., and Littleton, J. T. (2006). Expression profiling of a hypercontraction-induced myopathy in *Drosophila* suggests a compensatory cytoskeletal remodeling response. *J. Biol. Chem.* **281,** 8100–8109.

Nakamura, A., Harrod, G. V., and Davies, K. E. (2001). Activation of calcineurin and stress activated protein kinase/p38-mitogen activated protein kinase in hearts of utrophin-dystrophin knockout mice. *Neuromusc. Disord.* **11,** 251–259.

Nakamura, A., Yoshida, K., Takeda, S., Dohi, N., and Ikeda, S. (2002). Progression of dystrophic features and activation of mitogen-activated protein kinases and calcineurin by physical exercise, in hearts of *mdx* mice. *FEBS Lett.* **520,** 18–24.

Nakamura, A., Yoshida, K., Ueda, H., Takeda, S., and Ikeda, S. (2005). Up-regulation of mitogen activated protein kinases in *mdx* skeletal muscle following chronic treadmill exercise. *Biochim. Biophys. Acta* **1740,** 326–331.

Nawrotzki, R., Loh, N. Y., Ruegg, M. A., Davies, K. E., and Blake, D. J. (1998). Characterisation of α-dystrobrevin in muscle. *J. Cell Sci.* **111,** 2595–2605.

Neuman, S., Kaban, A., Volk, T., Yaffe, D., and Nudel, U. (2001). The dystrophin/utrophin homologues in *Drosphila* and in sea urchin. *Gene* **263,** 17–29.

Newey, S. E., Howman, E. V., Ponting, C. P., Benson, M. A., Nawrotzki, R., Loh, N. Y., Davies, K. E., and Blake, D. J. (2001). Syncoilin, a novel member of the intermediate filament superfamily that interacts with α-dystrobrevin in skeletal muscle. *J. Biol. Chem.* **276,** 6645–6655.

Nigro, V., Piluso, G., Belsito, A., Politano, L., Puca, A. A., Papparella, S., Rossi, E., Viglietto, G., Esposito, M. G., Abbondanza, C., Medici, N., Molinari, A. M., *et al.* (1996). Identification of a novel sarcoglycan gene at 5q33 encoding a sarcolemmal 35 kDa glycoprotein. *Hum. Mol. Genet.* **5,** 1179–1186.

Noguchi, S., McNally, E. M., Ben Othmane, K., Hagiwara, Y., Mizuno, Y., Yoshida, M., Yamamoto, H., Bönnemann, C. G., Gussoni, E., Denton, P. H., Kyriakides, T., Middleton, L., *et al.* (1995). Mutations in the dystrophin-associated protein γ-sarcoglycan in chromosome 13 muscular dystrophy. *Science* **270,** 819–822.

Oak, S. A., Russo, K., Petrucci, T. C., and Jarrett, H. W. (2001). Mouse α1-syntrophin binding to Grb2: Further evidence of a role for syntrophin in cell signaling. *Biochemistry* **40,** 11270–11278.

Oak, S. A., Zhou, Y. W., and Jarrett, H. W. (2003). Skeletal muscle signaling pathway through the dystrophin glycoprotein complex and Rac1. *J. Biol. Chem.* **278,** 39287–39295.

Ohlendieck, K., Ervasti, J. M., Matsumura, K., Kahl, S. D., Leveille, C. J., and Campbell, K. P. (1991). Dystrophin-related protein is localized to neuromuscular junctions of adult skeletal muscle. *Neuron* **7,** 499–508.

O'Neill, A., Williams, M. W., Resneck, W. G., Milner, D. J., Capetanaki, Y., and Bloch, R. J. (2002). Sarcolemmal organization in skeletal muscle lacking desmin: Evidence for cytokeratins associated with the membrane skeleton at costameres. *Mol. Biol. Cell* **13,** 2347–2359.

Pardo, J. V., D'Angelo Siliciano, J. V., and Craig, S. W. (1983). A vinculin-containing cortical lattice in skeletal muscle: Transverse lattice elements (''costameres'') mark sites of attachment between myofibrils and sarcolemma. *Proc. Natl. Acad. Sci. USA* **80,** 1008–1012.

Parsons, M. J., Campos, I., Hirst, E. M., and Stemple, D. L. (2002). Removal of dystroglycan causes severe muscular dystrophy in zebrafish embryos. *Development* **129,** 3505–3512.

Pastoret, C., and Sebille, A. (1993). Time course study of the isometric contractile properties of *mdx* mouse striated muscles. *J. Muscle Res. Cell Motil.* **14,** 423–431.

Patton, B. L., Miner, J. H., Chiu, A. Y., and Sanes, J. R. (1997). Distribution and function of laminins in the neuromuscular system of developing, adult, and mutant mice. *J. Cell Biol.* **139,** 1507–1521.

Paul, A. C., Sheard, P. W., Kaufman, S. J., and Duxson, M. J. (2002). Localization of α7 integrins and dystrophin suggests potential for both lateral and longitudinal transmission of tension in large mammalian muscles. *Cell Tissue Res.* **308,** 255–265.

Peng, H. B., Xie, H. B., Rossi, S. G., and Rotundo, R. L. (1999). Acetylcholinesterase clustering at the neuromuscular junction involves perlecan and dystroglycan. *J. Cell Biol.* **145,** 911–921.

Peter, A. K., and Crosbie, R. H. (2006). Hypertrophic response of Duchenne and limb-girdle muscular dystrophies is associated with activation of Akt pathway. *Exp. Cell Res.* **312,** 2580–2591.

Peters, M. F., Adams, M. E., and Froehner, S. C. (1997a). Differential association of syntrophin pairs with the dystrophin complex. *J. Cell Biol.* **138,** 81–93.

Peters, M. F., O'Brien, K. F., Sadoulet-Puccio, H. M., Kunkel, L. M., Adams, M. E., and Froehner, S. C. (1997b). β-Dystrobrevin, a new member of the dystrophin family—Identification, cloning, and protein associations. *J. Biol. Chem.* **272,** 31561–31569.

Peters, M. F., Sadoulet-Puccio, H. M., Grady, R. M., Kramarcy, N. R., Kunkel, L. M., Sanes, J. R., Sealock, R., and Froehner, S. C. (1998). Differential membrane localization and intermolecular associations of α-dystrobrevin isoforms in skeletal muscle. *J. Cell Biol.* **142,** 1269–1278.

Petrof, B. J., Shrager, J. B., Stedman, H. H., Kelly, A. M., and Sweeney, H. L. (1993). Dystrophin protects the sarcolemma from stresses developed during muscle contraction. *Proc. Natl. Acad. Sci. USA* **90,** 3710–3714.

Piluso, G., Mirabella, M., Ricci, E., Belsito, A., Abbondanza, C., Servidei, S., Puca, A. A., Tonali, P., Puca, G. A., and Nigro, V. (2000). γ1- and γ2-Syntrophins, two novel dystrophin-binding proteins localized in neuronal cells. *J. Biol. Chem.* **275,** 15851–15860.

Ponting, C. P., Blake, D. J., Davies, K. E., Kendrick-Jones, J., and Winder, S. J. (1996). ZZ and TAZ: New putative zinc fingers in dystrophin and other proteins. *Trends Biochem. Sci.* **21,** 11–13.

Poon, E., Howman, E. V., Newey, S. E., and Davies, K. E. (2002). Association of syncoilin and desmin: Linking intermediate filament proteins to the dystrophin-associated protein complex. *J. Biol. Chem.* **277,** 3433–3439.

Porter, G. A., Dmytrenko, G. M., Winkelmann, J. C., and Bloch, R. J. (1992). Dystrophin colocalizes with β-spectrin in distinct subsarcolemmal domains in mammalian skeletal muscle. *J. Cell Biol.* **117,** 997–1005.

Porter, J. D., Rafael, J. A., Ragusa, R. J., Brueckner, J. K., Trickett, J. I., and Davies, K. E. (1998). The sparing of extraocular muscle in dystrophinopathy is lost in mice lacking utrophin and dystrophin. *J. Cell Sci.* **111,** 1801–1811.

Puca, A. A., Nigro, V., Piluso, G., Belsito, A., Sampaolo, S., Quaderi, N., Rossi, E., Di Iorio, G., Ballabio, A., and Franco, B. (1998). Identification and characterization of a novel member of the dystrobrevin gene family. *FEBS Lett.* **425,** 7–13.

Quinlan, J. G., Johnson, S. R., McKee, M. K., and Lyden, S. P. (1992). Twitch and tetanus in mdx mouse muscle. *Muscle Nerve* **15,** 837–842.

Rafii, M. S., Hagiwara, H., Mercado, M. L., Seo, N. S., Xu, T., Dugan, T., Owens, R. T., Hook, M., McQuillan, D. J., Young, M. F., and Fallon, J. R. (2006). Biglycan binds to α- and γ-sarcoglycan and regulates their expression during development. *J. Cell Physiol.* **209,** 439–447.

Rando, T. A. (2001). The dystrophin–glycoprotein complex, cellular signaling, and the regulation of cell survival in the muscular dystrophies. *Muscle Nerve* **24,** 1575–1594.

Rentschler, S., Linn, H., Deininger, K., Bedford, M. T., Espanel, X., and Sudol, M. (1999). The WW domain of dystrophin requires EF-hands region to interact with β-dystroglycan. *Biol. Chem.* **380,** 431–442.

Rezniczek, G. A., Konieczny, P., Nikolic, B., Reipert, S., Schneller, D., Abrahamsberg, C., Davies, K. E., Winder, S. J., and Wiche, G. (2007). Plectin 1f scaffolding at the sarcolemma of dystrophic (*mdx*) muscle fibers through multiple interactions with β-dystroglycan. *J. Cell Biol.* **176,** 965–977.

Roberds, S. L., Anderson, R. D., Ibraghimov-Beskrovnaya, O., and Campbell, K. P. (1993). Primary structure and muscle-specific expression of the 50-kDa dystrophin-associated glycoprotein (adhalin). *J. Biol. Chem.* **268,** 23739–23742.

Roberts, R. G., and Bobrow, M. (1998). Dystrophins in vertebrates and invertebrates. *Hum. Mol. Genet.* **7,** 589–595.

Rosa, G., Ceccarini, M., Cavaldesi, M., Zini, M., and Petrucci, T. C. (1996). Localization of the dystrophin binding site at the carboxyl terminus of β-dystroglycan. *Biohem. Biophys. Res. Commun.* **223,** 272–277.

Rybakova, I. N., and Ervasti, J. M. (1997). Dystrophin–glycoprotein complex is monomeric and stabilizes actin filaments *in vitro* through a lateral association. *J. Biol. Chem.* **272,** 28771–28778.

Rybakova, I. N., Amann, K. J., and Ervasti, J. M. (1996). A new model for the interaction of dystrophin with F-actin. *J. Cell Biol.* **135,** 661–672.

Rybakova, I. N., Patel, J. R., and Ervasti, J. M. (2000). The dystrophin complex forms a mechanically strong link between the sarcolemma and costameric actin. *J. Cell Biol.* **150,** 1209–1214.

Rybakova, I. N., Patel, J. R., Davies, K. E., Yurchenco, P. D., and Ervasti, J. M. (2002). Utrophin binds laterally along actin filaments and can couple costameric actin with the sarcolemma when overexpressed in dystrophin-deficient muscle. *Mol. Biol. Cell* **13,** 1512–1521.

Rybakova, I. N., Humston, J. M., Sonnemann, K. J., and Ervasti, J. M. (2006). Dystrophin and utrophin bind actin filaments through distinct modes of contact. *J. Biol. Chem.* **281,** 9996–10001.

Sacco, P., Jones, D. A., Dick, J. R., and Vrbova, G. (1992). Contractile properties and susceptibility to exercise-induced damage of normal and *mdx* mouse tibialis anterior muscle. *Clin. Sci. (Lond.)* **82,** 227–236.

Sadoulet-Puccio, H. M., Khurana, T. S., Cohen, J. B., and Kunkel, L. M. (1996). Cloning and characterization of the human homologue of a dystrophin related phosphoprotein found at the *Torpedo* electric organ post-synaptic membrane. *Hum. Mol. Genet.* **5,** 489–496.

Sadoulet-Puccio, H. M., Rajala, M., and Kunkel, L. M. (1997). Dystrobrevin and dystrophin: An interaction through coiled-coil motifs. *Proc. Natl. Acad. Sci. USA* **94,** 12413–12418.

Samitt, C. E., and Bonilla, E. (1990). Immunocytochemical study of dystrophin at the myotendinous junction. *Muscle Nerve* **13,** 493–500.

Sander, M., Chavoshan, B., Harris, S. A., Iannaccone, S. T., Stull, J. T., Thomas, G. D., and Victor, R. G. (2000). Functional muscle ischemia in neuronal nitric oxide synthase-deficient skeletal muscle of children with Duchenne muscular dystrophy. *Proc. Natl. Acad. Sci. USA* **97,** 13818–13823.

Sasaoka, T., Imamura, M., Araishi, K., Noguchi, S., Mizuno, Y., Takagoshi, N., Hama, H., Wakabayashi-Takai, E., Yoshimoto-Matsuda, Y., Nonaka, I., Kaneko, K., Yoshida, M., *et al.* (2003). Pathological analysis of muscle hypertrophy and degeneration in muscular dystrophy in γ-sarcoglycan-deficient mice. *Neuromuscul. Disord.* **13,** 193–206.

Schroder, R., Mundegar, R. R., Treusch, M., Schlegel, U., Blumcke, I., Owaribe, K., and Magin, T. M. (1997). Altered distribution of plectin/HD1 in dystrophinopathies. *Eur. J. Cell Biol.* **74,** 165–171.

Sealock, R., Butler, M. H., Kramarcy, N. R., Gao, K.-X., Murname, A. A., Douville, K., and Froehner, S. C. (1991). Localization of dystrophin relative to acetylcholine receptor domains in electric tissue and adult and cultured skeletal muscle. *J. Cell Biol.* **113,** 1133–1144.

Segalat, L., Grisoni, K., Archer, J., Vargas, C., Bertrand, A., and Anderson, J. E. (2005). CAPON expression in skeletal muscle is regulated by position, repair, NOS activity, and dystrophy. *Exp. Cell Res.* **302,** 170–179.

Senter, L., Luise, M., Presotto, C., Betto, R., Teresi, A., Ceoldo, S., and Salviati, G. (1993). Interaction of dystrophin with cytoskeletal proteins: Binding to talin and actin. *Biochem. Biophys. Res. Commun.* **192,** 899–904.

Shcherbata, H. R., Yatsenko, A. S., Patterson, L., Sood, V. D., Nudel, U., Yaffe, D., Baker, D., and Ruohola-Baker, H. (2007). Dissecting muscle and neuronal disorders in a Drosophila model of muscular dystrophy. *EMBO J.* **26,** 481–493.

Shear, C. R., and Bloch, R. J. (1985). Vinculin in subsarcolemmal densities in chicken skeletal muscle: Localization and relationship to intracellular and extracellular structures. *J. Cell Biol.* **101,** 240–256.

Shiga, K., Yoshioka, H., Matsumiya, T., Kimura, I., Takeda, S., and Imamura, M. (2006). Zeta-sarcoglycan is a functional homologue of gamma-sarcoglycan in the formation of the sarcoglycan complex. *Exp. Cell Res.* **312,** 2083–2092.

Smalheiser, N. R., and Kim, E. (1995). Purification of cranin, a laminin binding membrane protein: Identity with dystroglycan and reassessment of its carbohydrate moieties. *J. Biol. Chem.* **270,** 15425–15433.

Sonnemann, K. J., Fitzsimons, D. P., Patel, J. R., Liu, Y., Schneider, M. F., Moss, R. L., and Ervasti, J. M. (2006). Cytoplasmic γ-actin is not required for skeletal muscle development but its absence leads to a progressive myopathy. *Dev. Cell* **11,** 387–397.

Spence, H. J., Dhillon, A. S., James, M., and Winder, S. J. (2004). Dystroglycan, a scaffold for the ERK-MAP kinase cascade. *EMBO Rep.* **5,** 484–489.

Stedman, H. H., Sweeney, H. L., Shrager, J. B., Maguire, H. C., Panettieri, R. A., Petrof, B., Narusawa, M., Leferovich, J. M., Sladky, J. T., and Kelly, A. M. (1991). The mdx mouse diaphragm reproduces the degenerative changes of Duchenne muscular dystrophy. *Nature* **352,** 536–539.

Steffen, L. S., Guyon, J. R., Vogel, E. D., Beltre, R., Pusack, T. J., Zhou, Y., Zon, L. I., and Kunkel, L. M. (2007). Zebrafish orthologs of human muscular dystrophy genes. *BMC Genomics* **8,** 79.

Stevens, E. D., and Faulkner, J. A. (2000). The capacity of mdx mouse diaphragm muscle to do oscillatory work. *J. Physiol.* **522(Pt. 3),** 457–466.

Stone, M. R., O'Neill, A., Catino, D., and Bloch, R. J. (2005). Specific interaction of the actin-binding domain of dystrophin with intermediate filaments containing keratin 19. *Mol. Biol. Cell* **16,** 4280–4293.

Stossel, T. P., Condeelis, J., Cooley, L., Hartwig, J. H., Noegel, A., Schleicher, M., and Shapiro, S. S. (2001). Filamins as integrators of cell mechanics and signalling. *Nat. Rev. Mol. Cell. Biol.* **2,** 138–145.

Straub, V., Bittner, R. E., Léger, J. J., and Voit, T. (1992). Direct visualization of the dystrophin network on skeletal muscle fiber membrane. *J. Cell Biol.* **119,** 1183–1191.

Straub, V., Rafael, J. A., Chamberlain, J. S., and Campbell, K. P. (1997). Animal models for muscular dystrophy show different patterns of sarcolemmal disruption. *J. Cell Biol.* **139,** 375–385.

Straub, V., Donahue, K. M., Allamand, V., Davisson, R. L., Kim, Y. R., and Campbell, K. P. (2000). Contrast agent-enhanced magnetic resonance imaging of skeletal muscle damage in animal models of muscular dystrophy. *Magn. Reson. Med.* **44,** 655–659.

Street, S. F. (1983). Lateral transmission of tension in frog myofibers: A myofibrillar network and transverse cytoskeletal connections are possible transmitters. *J. Cell Physiol.* **114,** 346–364.

Sugiyama, J., Bowen, D. C., and Hall, Z. W. (1994). Dystroglycan binds nerve and muscle agrin. *Neuron* **13,** 103–115.

Sunada, Y., Bernier, S. M., Kozak, C. A., Yamada, Y., and Campbell, K. P. (1994). Deficiency of merosin in dystrophic *dy* mice and genetic linkage of laminin M chain gene to *dy* locus. *J. Biol. Chem.* **269,** 13729–13732.

Suzuki, A., Yoshida, M., Yamamoto, H., and Ozawa, E. (1992). Glycoprotein-binding site of dystrophin is confined to the cysteine-rich domain and the first half of the carboxy-terminal domain. *FEBS Lett.* **308,** 154–160.

Suzuki, A., Yoshida, M., Hayashi, K., Mizuno, Y., Hagiwara, Y., and Ozawa, E. (1994). Molecular organization at the glycoprotein-complex-binding site of dystrophin—Three dystrophin-associated proteins bind directly to the carboxy-terminal portion of dystrophin. *Eur. J. Biochem.* **220,** 283–292.

Suzuki, A., Yoshida, M., and Ozawa, E. (1995). Mammalian α1- and β1-syntrophin bind to the alternative splice-prone region of the dystrophin COOH terminus. *J. Cell Biol.* **128,** 373–381.

Talts, J. F., Andac, Z., Gohring, W., Brancaccio, A., and Timpl, R. (1999). Binding of the G domains of laminin α1 and α2 chains and perlecan to heparin, sulfatides, α-dystroglycan and several extracellular matrix proteins. *EMBO J.* **18,** 863–870.

Thomas, G. D., Sander, M., Lau, K. S., Huang, P. L., Stull, J. T., and Victor, R. G. (1998). Impaired metabolic modulation of α-adrenergic vasoconstriction in dystrophin-deficient skeletal muscle. *Proc. Natl. Acad. Sci. USA* **95,** 15090–15095.

Thomas, G. D., Shaul, P. W., Yuhanna, I. S., Froehner, S. C., and Adams, M. E. (2003). Vasomodulation by skeletal muscle-derived nitric oxide requires α-syntrophin-mediated sarcolemmal localization of neuronal nitric oxide synthase. *Circ. Res.* **92,** 554–560.

Thompson, T. G., Chan, Y. M., Hack, A. A., Brosius, M., Rajala, M., Lidov, H. G., McNally, E. M., Watkins, S., and Kunkel, L. M. (2000). Filamin 2 (FLN2): A muscle-specific sarcoglycan interacting protein. *J. Cell Biol.* **148,** 115–126.

Tidball, J. G., and Law, D. J. (1991). Dystrophin is required for normal thin filament-membrane associations at myotendinous junctions. *Am. J. Pathol.* **138,** 17–21.

Tinsley, J. M., Blake, D. J., Roche, A., Byth, B. C., Knight, A. E., Kendrick-Jones, J., Suthers, G. K., Love, D. R., Edwards, Y. H., and Davies, K. E. (1992). Primary structure of dystrophin-related protein. *Nature* **360,** 591–593.

Tinsley, J. M., Potter, A. C., Phelps, S. R., Fisher, R., Trickett, J. I., and Davies, K. E. (1996). Amelioration of the dystrophic phenotype of *mdx* mice using a truncated utrophin transgene. *Nature* **384,** 349–353.

Tinsley, J., Deconinck, N., Fisher, R., Kahn, D., Phelps, S., Gillis, J. M., and Davies, K. (1998). Expression of full-length utrophin prevents muscular dystrophy in *mdx* mice. *Nat. Med.* **4,** 1441–1444.

Towers, P. R., Lescure, P., Baban, D., Malek, J. A., Duarte, J., Jones, E., Davies, K. E., Segalat, L., and Sattelle, D. B. (2006). Gene expression profiling studies on *Caenorhabditis elegans* dystrophin mutants dys-1(cx-35) and dys-1(cx18). *Genomics* **88,** 642–649.

Ursitti, J. A., Lee, P. C., Resneck, W. G., McNally, M. M., Bowman, A. L., O'Neill, A., Stone, M. R., and Bloch, R. J. (2004). Cloning and characterization of cytokeratins 8 and 19 in adult rat striated muscle. Interaction with the dystrophin glycoprotein complex. *J. Biol. Chem.* **279,** 41830–41838.

Vachon, P. H., Xu, H., Liu, L., Loechel, F., Hayashi, Y., Arahata, K., Reed, J. C., Wewer, U. M., and Engvall, E. (1997). Integrins ($\alpha 7\beta 1$) in muscle function and survival—Disrupted expression in merosin-deficient congenital muscular dystrophy. *J. Clin. Invest.* **100,** 1870–1881.

Vandebrouck, A., Sabourin, J., Rivet, J., Balghi, H., Sebille, S., Kitzis, A., Raymond, G., Cognard, C., Bourmeyster, N., and Constantin, B. (2007). Regulation of capacitative calcium entries by α1-syntrophin: Association of TRPC1 with dystrophin complex and the PDZ domain of alpha1-syntrophin. *FASEB J.* **21,** 608–617.

van der Plas, M. C., Pilgram, G. S., Plomp, J. J., de Jong, A., Fradkin, L. G., and Noordermeer, J. N. (2006). Dystrophin is required for appropriate retrograde control of neurotransmitter release at the Drosophila neuromuscular junction. *J. Neurosci.* **26,** 333–344.

Vilquin, J. T., Brussee, V., Asselin, I., Kinoshita, I., Gingras, M., and Tremblay, J. P. (1998). Evidence of *mdx* mouse skeletal muscle fragility *in vivo* by eccentric running exercise. *Muscle Nerve* **21,** 567–576.

Wagner, K. R., Cohen, J. B., and Huganir, R. L. (1993). The 87K postsynaptic membrane protein from Torpedo is a protein-tyrosine kinase substrate homologous to dystrophin. *Neuron* **10,** 511–522.

Warner, L. E., DelloRusso, C., Crawford, R. W., Rybakova, I. N., Patel, J. R., Ervasti, J. M., and Chamberlain, J. S. (2002). Expression of Dp260 in muscle tethers the actin cytoskeleton to the dystrophin–glycoprotein complex. *Hum. Mol. Genet.* **11,** 1095–1105.

Way, M., Pope, B., Cross, R. A., Kendrick-Jones, J., and Weeds, A. G. (1992). Expression of the N-terminal domain of dystrophin in *E. coli* and demonstration of binding to F-actin. *FEBS Lett.* **301,** 243–245.

Wehling, M., Spencer, M. J., and Tidball, J. G. (2001). A nitric oxide synthase transgene ameliorates muscular dystrophy in *mdx* mice. *J. Cell Biol.* **155,** 123–131.

Weller, B., Karpati, G., and Carpenter, S. (1990). Dystrophin-deficient *mdx* muscle fibers are preferentially vulnerable to necrosis induced by experimental lengthening contractions. *J. Neurol. Sci.* **100,** 9–13.

Wheeler, M. T., Zarnegar, S., and McNally, E. M. (2002). Zeta-sarcoglycan, a novel component of the sarcoglycan complex, is reduced in muscular dystrophy. *Hum. Mol. Genet.* **11,** 2147–2154.

Williams, M. W., and Bloch, R. J. (1999). Extensive but coordinated reorganization of the membrane skeleton in myofibers of dystrophic (*mdx)* mice. *J. Cell Biol.* **144,** 1259–1270.

Woods, C. E., Novo, D., DiFranco, M., and Vergara, J. L. (2004). The action potential-evoked sarcoplasmic reticulum calcium release is impaired in *mdx* mouse muscle fibres. *J. Physiol.* **557,** 59–75.

Woods, C. E., Novo, D., DiFranco, M., Capote, J., and Vergara, J. L. (2005). Propagation in the transverse tubular system and voltage dependence of calcium release in normal and *mdx* mouse muscle fibres. *J. Physiol.* **568,** 867–880.

Xiong, D., Yajima, T., Lim, B. K., Stenbit, A., Dublin, A., Dalton, N. D., Summers-Torres, D., Molkentin, J. D., Duplain, H., Wessely, R., Chen, J., and Knowlton, K. U. (2007). Inducible cardiac-restricted expression of enteroviral protease 2A is sufficient to induce dilated cardiomyopathy. *Circulation* **115,** 94–102.

Xu, H., Christmas, P., Wu, X.-R., Wewer, U. M., and Engvall, E. (1994). Defective muscle basement membrane and lack of M-laminin in the dystrophic *dy/dy* mouse. *Proc. Natl. Acad. Sci. USA* **91,** 5572–5576.

Yang, B. O., Ibraghimov-Beskrovnaya, O., Moomaw, C. R., Slaughter, C. A., and Campbell, K. P. (1994). Heterogeneity of the 59-kDa dystrophin-associated protein revealed by cDNA cloning and expression. *J. Biol. Chem.* **269,** 6040–6044.

Yang, B., Jung, D., Motto, D., Meyer, J., Koretzky, G., and Campbell, K. P. (1995a). SH3 domain-mediated interaction of dystroglycan and Grb2. *J. Biol. Chem.* **270,** 11711–11714.

Yang, B., Jung, D., Rafael, J. A., Chamberlain, J. S., and Campbell, K. P. (1995b). Identification of α-syntrophin binding to syntrophin triplet, dystrophin, and utrophin. *J. Biol. Chem.* **270,** 4975–4978.

Yasuda, S., Townsend, D., Michele, D. E., Favre, E. G., Day, S. M., and Metzger, J. M. (2005). Dystrophic heart failure blocked by membrane sealant poloxamer. *Nature* **436,** 1025–1029.

Yokota, T., Lu, Q. L., Morgan, J. E., Davies, K. E., Fisher, R., Takeda, S., and Partridge, T. A. (2006). Expansion of revertant fibers in dystrophic *mdx* muscles reflects activity of muscle precursor cells and serves as an index of muscle regeneration. *J. Cell Sci.* **119,** 2679–2687.

Yoshida, M., and Ozawa, E. (1990). Glycoprotein complex anchoring dystrophin to sarcolemma. *J. Biochem.* **108,** 748–752.

Yoshida, M., Suzuki, A., Yamamoto, H., Noguchi, S., Mizuno, Y., and Ozawa, E. (1994). Dissociation of the complex of dystrophin and its associated proteins into several unique groups by *n*-octyl β-D-glucoside. *Eur. J. Biochem.* **222,** 1055–1061.

Yoshida, M., Yamamoto, H., Noguchi, S., Mizuno, Y., Hagiwara, Y., and Ozawa, E. (1995). Dystrophin-associated protein A0 is a homologue of the *Torpedo* 87K protein. *FEBS Lett.* **367,** 311–314.

Yoshida, M., Hama, H., Ishikawa-Sakurai, M., Imamura, M, Mizuno, Y., Araishi, K., Wakabayashi-Takai, E., Noguchi, S., Sasaoka, T., and Ozawa, E. (2000). Biochemical evidence for association of dystrobrevin with the sarcoglycan-sarcospan complex as a basis for understanding sarcoglycanopathy. *Hum. Mol. Genet.* **9,** 1033–1040.

Zhou, Y. W., Thomason, D. B., Gullberg, D., and Jarrett, H. W. (2006). Binding of laminin α1-chain LG4–5 domain to α-dystroglycan causes tyrosine phosphorylation of syntrophin to initiate Rac1 signaling. *Biochemistry* **45,** 2042–2052.