Muscular dystrophies involving the dystrophin–glycoprotein complex: an overview of current mouse models
Madeleine Durbeej and Kevin P Campbell*

The dystrophin–glycoprotein complex (DGC) is a multisubunit complex that connects the cytoskeleton of a muscle fiber to its surrounding extracellular matrix. Mutations in the DGC disrupt the complex and lead to muscular dystrophy. There are a few naturally occurring animal models of DGC-associated muscular dystrophy (e.g. the dystrophin-deficient mdx mouse, dystrophic golden retriever dog, HFMD cat and the δ-sarcoglycan-deficient BIO 14.6 cardiomyopathic hamster) that share common genetic protein abnormalities similar to those of the human disease. However, the naturally occurring animal models only partially resemble human disease. In addition, no naturally occurring mouse models associated with loss of other DGC components are available. This has encouraged the generation of genetically engineered mouse models for DGC-linked muscular dystrophy. Not only have analyses of these mice led to a significant improvement in our understanding of the pathogenetic mechanisms for the development of muscular dystrophy, but they will also be immensely valuable tools for the development of novel therapeutic approaches for these incapacitating diseases.

Abbreviations
CMD congenital muscular dystrophy
DGC dystrophin–glycoprotein complex
DMD/BMD Duchenne or Becker muscular dystrophy
FCMD Fukuyama congenital muscular dystrophy
HFMD hypertrophic feline muscular dystrophy
LGMD limb–girdle muscular dystrophy
Mdx X-chromosome-linked muscular dystrophy
MEB muscle–eye–brain disease
myd myodystrophy
nNOS neuronal nitric oxide synthase

Introduction
Muscular dystrophy is a general term that describes a group of inherited and gradually debilitating myogenic disorders. Genetically, the pattern of inheritance can be X-linked recessive as in Duchenne or Becker muscular dystrophy (DMD/BMD), autosomal dominant as in limb–girdle muscular dystrophy type 1 (LGMD type 1), or autosomal recessive as in limb–girdle muscular dystrophy type 2 (LGMD type 2). DMD is the most common type of muscular dystrophy affecting approximately 1 out of 3500 males whereas the limb–girdle muscular dystrophies affect roughly 1 out of 20,000. Clinically, the muscular dystrophies are a heterogeneous group of disorders. Patients with DMD have a childhood onset phenotype and die by their early twenties as a result of either respiratory or cardiac failure, whereas patients with BMD have moderate weakness in adulthood and may have normal life spans. The limb–girdle muscular dystrophies have a highly variable onset and progression, but the unifying theme among the limb–girdle muscular dystrophies is the initial involvement of the shoulder and pelvic girdle muscles. Moreover, muscular dystrophies may or may not be associated with cardiomyopathy [1–4].

Combined positional cloning and candidate gene approaches have been used to identify an increasing number of genes that are mutated in various forms of muscular dystrophy. According to the genetic basis, muscular dystrophies have now been reclassified and close to 30 genes have been implicated to cause muscular dystrophy (see [5] for review; see also Table 1). The first gene to be cloned was the dystrophin gene that is mutated in DMD and BMD [6]. Soon after the discovery of dystrophin, the dystrophin–glycoprotein complex (DGC) was identified and these studies opened up a new avenue of muscular dystrophy research [7–9]. Within the past couple of years, several targeted mouse models for DGC-associated muscular dystrophy have been generated and these mouse models, which are the focus of this review, have significantly contributed to understanding the pathogenetic mechanisms of muscular dystrophy.

Dystrophin–glycoprotein complex
The DGC is a large complex of membrane-associated proteins that is critical for the integrity of skeletal muscle fibers. This complex consists of dystrophin, the dystroglycans (α and β), the sarcoglycans (α, β, γ and δ), sarcospan, the syntrophins (α1, β1, β2; γ1- and γ2-syntrophins have been identified in neurons) and α-dystrobrevin [7,8,10–21]. Dystrophin binds to cytoskeletal actin and to the transmembrane protein β-dystroglycan; the extracellular domain of β-dystroglycan binds to the peripheral membrane protein, α-dystroglycan; and α-dystroglycan binds laminin-2 in the basal lamina [22–24] (see Figure 1). Furthermore, α-dystroglycan has been shown to bind the heparane sulfate proteoglycans agrin and perlecan and to the chondroitin sulfate proteoglycan biglycan [25–28]. In addition, α-dystroglycan was recently shown to bind neurexin in neurons [29]. Perlecan and agrin are, along with laminin-2, also present in the basement membrane of the skeletal muscle. Thus, the DGC serves as a link between the extracellular matrix and the subsarcolemmal cytoskeleton and the DGC is thought to protect muscle cells from contraction-induced damage [30–31]. In agreement with this hypothesis, mutations in...
genes encoding dystrophin, all four sacroglycans and the
laminin α2 chain are responsible for DMD/BMD, limb–girdle
muscular dystrophy type 2C-F and congenital muscular
dystrophy (CMD), respectively [6,11,14–17,32,33]. Not only
does the DGC have structural roles but it may also play a role
in signaling. Several signaling molecules bind DGC core
components. Grb2, a signal transduction adapter protein,
binds β-dystroglycan [34]. The filamins have been implicated
as signal transducers and a member of the filamin family, fil-
amin 2, interacts with γ and δ-sarcoglycan [35]. Furthermore,
dystrophin interacts with two classes of cytoplasmic mole-
cules, the syntrophins [36,37] and dystrobrevins, which have
been implicated in signaling [21]. α1-syntrophin contains a
PDZ-domain (a protein–protein interaction motif) that inter-
acts with at least two sarcolemmal proteins involved in signal
transduction, neuronal nitric oxide synthase (nNOS) [38] and
voltage-gated sodium channels [39,40]. Similarly, the PDZ-
domain of β2-syntrophin (expressed at the neuromuscular
junction where it binds the dystrophin homologue utrophin)
interacts with the PDZ-domain-containing microtubule-
associated serine/threonine kinases MAST205 and SAST
[41]. α-dystrobrevin binds syntrophins in addition to
dystrophin and is a substrate for tyrosine kinases [42,43].
Moreover, biochemical evidence was recently presented for

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mode of inheritance and gene locus</th>
<th>Gene product</th>
<th>Mouse models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne/Becker MD</td>
<td>XR Xp21</td>
<td>Dystrophin</td>
<td>Mdx</td>
</tr>
<tr>
<td>Emery–Dreifuss MD</td>
<td>XR Xp28</td>
<td>Emerin</td>
<td>–</td>
</tr>
<tr>
<td>LGMD 1A</td>
<td>AD 5q31</td>
<td>Myotilin</td>
<td>–</td>
</tr>
<tr>
<td>LGMD 1B</td>
<td>AD 1q11</td>
<td>Lamin A/C</td>
<td>Lmna&lt;sup&gt;−/−&lt;/sup&gt; [121]</td>
</tr>
<tr>
<td>LGMD 1C</td>
<td>AD 3p25</td>
<td>Caveolin-3</td>
<td>Cav3&lt;sup&gt;−/−&lt;/sup&gt;</td>
</tr>
<tr>
<td>LGMD 1D</td>
<td>AD 6q23</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>LGMD 1E</td>
<td>AD 7q32</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>LGMD 1F</td>
<td>AD 5q31</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>LGMD 2A</td>
<td>AR 15q15</td>
<td>Calpain-3</td>
<td>Capn3&lt;sup&gt;−/−&lt;/sup&gt; [122]</td>
</tr>
<tr>
<td>LGMD 2B</td>
<td>AR 2p13</td>
<td>Dysterlin</td>
<td>SJL [123]</td>
</tr>
<tr>
<td>LGMD 2C</td>
<td>AR 13q12</td>
<td>γ-sarcoglycan</td>
<td>Sgcγ</td>
</tr>
<tr>
<td>LGMD 2D</td>
<td>AR 17q12</td>
<td>α-sarcoglycan</td>
<td>Sgcα</td>
</tr>
<tr>
<td>LGMD 2E</td>
<td>AR 4q12</td>
<td>β-sarcoglycan</td>
<td>Sgcβ&lt;sup&gt;−/−&lt;/sup&gt;</td>
</tr>
<tr>
<td>LGMD 2F</td>
<td>AR 5q33</td>
<td>δ-sarcoglycan</td>
<td>Sgcd&lt;sup&gt;−/−&lt;/sup&gt;</td>
</tr>
<tr>
<td>LGMD 2G</td>
<td>AR 17q11</td>
<td>Telethonin</td>
<td>–</td>
</tr>
<tr>
<td>LGMD 2H</td>
<td>AR 9q31</td>
<td>TRIM31 [124]</td>
<td>–</td>
</tr>
<tr>
<td>LGMD 2I</td>
<td>AR 19q13</td>
<td>Fukutin-related protein [125]</td>
<td>–</td>
</tr>
<tr>
<td>Miyoshi myopathy</td>
<td>AR 2p13</td>
<td>Dysterlin</td>
<td>SJL [123]</td>
</tr>
<tr>
<td>Tibial MD</td>
<td>AD 2q31</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>Classical or pure CMD</td>
<td>AR 6q22</td>
<td>Laminin α2</td>
<td>dy</td>
</tr>
<tr>
<td>Fukuyama CMD</td>
<td>AR 9q31</td>
<td>Fukutin</td>
<td>–</td>
</tr>
<tr>
<td>MDC1C</td>
<td>AR 19q13</td>
<td>Fukutin-related protein [125]</td>
<td>–</td>
</tr>
<tr>
<td>α? integrin CMD</td>
<td>AR 12q13</td>
<td>α? integrin</td>
<td>Itgbα7&lt;sup&gt;−/−&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ulrich CMD</td>
<td>AR ?</td>
<td>Collagen VI α2 [126]</td>
<td>–</td>
</tr>
<tr>
<td>Rigid spine CMD</td>
<td>AR 1p35</td>
<td>Selenoprotein N [128]</td>
<td>–</td>
</tr>
<tr>
<td>Muscle–eye–brain disease</td>
<td>AR 1p32</td>
<td>POMGnT1</td>
<td>–</td>
</tr>
<tr>
<td>Emery–Dreifuss MD</td>
<td>AD 1q11</td>
<td>Lamin A/C</td>
<td>Lmna&lt;sup&gt;−/−&lt;/sup&gt; [121]</td>
</tr>
<tr>
<td>Bethlem myopathy</td>
<td>AD 21q22</td>
<td>Collagen V1 α1</td>
<td>Col16a1&lt;sup&gt;−/−&lt;/sup&gt; [129]</td>
</tr>
<tr>
<td>Bethlem myopathy</td>
<td>AD 21q22</td>
<td>Collagen V1 α2</td>
<td>–</td>
</tr>
<tr>
<td>Bethlem myopathy</td>
<td>AD 2q37</td>
<td>Collagen V1 α3</td>
<td>–</td>
</tr>
<tr>
<td>?</td>
<td>?</td>
<td>Collagen XV [130]</td>
<td>Col15α1&lt;sup&gt;−/−&lt;/sup&gt;</td>
</tr>
<tr>
<td>EB and MD</td>
<td>AR 8q24</td>
<td>Pleckin</td>
<td>Pleckin&lt;sup&gt;−/−&lt;/sup&gt; [131]</td>
</tr>
<tr>
<td>Facioscapulohumeral MD</td>
<td>AD 4q35</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>Scapuloperoneal MD</td>
<td>AD 12q21</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>Oculopharyngeal MD</td>
<td>AD 14q11.2</td>
<td>Poly A binding protein 2</td>
<td>–</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>AD 19q13</td>
<td>Myotonin-protein kinase/Six5</td>
<td>Six5&lt;sup&gt;−/−&lt;/sup&gt; [132,133]</td>
</tr>
</tbody>
</table>

A summary list of muscular dystrophies, their Mendelian inheritance pattern, chromosomal location, mutated proteins and available mouse models. MD, muscular dystrophy; LGMD, limb–girdle muscular dystrophy; CMD, congenital muscular dystrophy; EB, epidermolysis bullosa; XR, X-linked recessive; AD, autosomal dominant; AR, autosomal recessive. For primary references on the muscular dystrophies, their mode of inheritance, gene locus, mutated proteins and available mouse models, please see [5] and main text.
an association of α-dystrobrevin with the sarcoglycan–sarcospan complex, indicating that the sarcoglycan complex is linked to nNOS signaling via α-syntrophin/α-dystrobrevin [44].

All vertebrates seem to have well-defined sequences encoding dystrophin and its homologues, utrophin and DRP-2. Dystrophin-like sequences have also been identified in invertebrates such as amphioxus, sea squirt, starfish, scallop, fruit fly and nematode [45]. In each case, phylogenetic analyses showed the invertebrate dystrophins to be orthologues of the last common ancestor of dystrophin, utrophin and DRP-2. Given the diversity of the remainder of the components of the vertebrate DGC, how much simpler is the invertebrate counterpart? The release of the complete sequences of the Drosophila melanogaster and Caenorhabditis elegans genomes have afforded the opportunity to assess the invertebrate repertoire of the DGC, using a combination of in vitro and in silico techniques [46,47] (Table 2). In summary, seventeen known human/mouse components (three dystrophin-related proteins, two dystrobrevins, five sarcoglycans, five syntrophins, one dystroglycan and one sarcospan) appear to be reduced to eight in Drosophila (one dystrophin, one dystrobrevin, three sarcoglycans, two syntrophins, one dystroglycan and no sarcospan) [46]. Furthermore, C. elegans retains all essential human/mouse counterparts of the DGC, but with less diversity [47].

Among the DGC components, only dystrophin and the sarcoglycans are linked to muscular dystrophy. To date, no human mutations have been found in dystroglycan, sarcospan, the syntrophins or the dystrobrevins. Mouse models for each of the core components of the DGC exist, however, and each mouse model (for a summary, see Table 3) will be discussed in relationship to muscular dystrophy.

Animal models for deficiency of dystrophin and dystrophin-binding proteins

Dystrophin

The mdx (X-chromosome-linked muscular dystrophy) mouse is the best-characterized mouse model for muscular dystrophy: >500 papers have been published in its analysis.
As a result of a point mutation in exon 23 of the dystrophin gene, the \textit{mdx} mouse is missing dystrophin \cite{48}. Absence of dystrophin in skeletal muscle also affects the expression of the other DGC components at the sarcolemma \cite{49}. Although this mouse has proved to be a valuable model for DMD, the progressive muscle-wasting disease presents itself in a much milder form than in humans \cite{50} at least in certain muscles. The most affected muscle in the \textit{mdx} mouse is the diaphragm, which reproduces the degenerative changes of muscular dystrophy \cite{51} and the specific twitch force, specific tetanic force and maximum power are all significantly reduced in diaphragm \cite{52}. The \textit{mdx} mice show signs of muscular dystrophy in other muscles during their first six week of life but subsequently show little weakness and have a near-normal lifespan. This partial ‘recovery’ is as a result of substantial regeneration. The \textit{mdx} mouse adapts to muscle degeneration with an expansion of the satellite cell population and muscle hypertrophy. Transcription factors seem to be important for this successful regeneration. \textit{Mdx} mice lacking the muscle-specific transcription factor MyoD show a more severe dystrophy due to a deficiency in regenerative capabilities of the muscle \cite{53}. Likewise, \textit{mdx} mice deficient in the myocyte nuclear factor, which is selectively expressed in satellite cells, exhibit an exacerbated dystrophic phenotype as a result of satellite-cell dysfunction \cite{54}.

Another possible explanation for the mild phenotype of the \textit{mdx} mouse is that the homologous protein utrophin compensates for the lack of dystrophin. Indeed, mice lacking both dystrophin and utrophin show many signs of DMD in humans: they have a reduced life-span (dying between 4 and 20 weeks), they suffer from severe muscle weakness with joint contractures, pronounced growth retardation, kyphosis and cardiomyopathy, suggesting that dystrophin and utrophin play complementary roles \cite{55,56}. The dystrophic phenotype of the utrn–/–/\textit{mdx} mouse was subsequently ameliorated by skeletal-muscle-specific expression of truncated utrophin, indicating that utrn–/–/\textit{mdx} mice succumb to a skeletal muscle defect and that their reduced life-span is not as a result of either

\begin{table}[h]
\begin{center}
\begin{tabular}{|l|l|l|l|l|}
\hline
Protein & \textit{Mus musculus} & \textit{Drosophila} & \textit{C. elegans} & \textit{Danio rerio} \\
\hline
Dystroglycan & X86073 & AF277390 & Z68011 & BF157619 \\
\hline
ζ-sarcoglycan & AF064081 & AF277391 & ? & ? \\
\hline
β-sarcoglycan & AF169298 & AF277392 & AF099925 & AA495110 \\
\hline
γ-sarcoglycan & AF282901 & AF277393 & Z68314 & ? \\
\hline
δ-sarcoglycan & AF024923 & AF277393 & Z68314 & AJ877617 \\
\hline
ε-sarcoglycan & AF031919 & AF277391 & AF07754 & AW281123 \\
\hline
\hline
Dystrophin and homologues & Dystrophin (DYS) & Dystrophin (dys-1) & Dystrophin & Dystrophin \\
\hline

\end{tabular}
\end{center}
\caption{DGC components in various organisms.}
\end{table}

\footnotesize

* Human sequences. A summary list of DGC sequences from mouse, fruitfly, nematode and zebrafish. Accession (Acc) numbers (underlined) were extracted from GenBank entries for genomic and cDNA clones (see also \cite{46,47}).
cardiac or neurogenic components [57]. Although the mdx mouse has the capability to adapt to muscle degeneration and utrophin to some extent can compensate for the loss of dystrophin, it should be noted that the serum levels of creatine kinase are elevated in these mice [58], which is a typical diagnostic criteria for muscular dystrophies.

Other than dystrophin, several shorter isoforms are also generated from the dystrophin gene through differential promoter usage. Transcripts from four internal dystrophin promoters produce proteins of 260, 140, 116 and 71 kDa (Dp260, Dp140, Dp116, Dp71) [59–62]. Dp260 is expressed predominantly in retina [61]. Dp140 is localized in brain and kidney [62,63] and Dp116 is expressed exclusively in Schwann cells [59]. Dp71 is expressed at high levels in almost all tissues except skeletal muscle [60]. Yet, mice with a targeted inactivation of Dp71 display no obvious phenotype [64]. The mdx<sup>2cv-5cv</sup> are other mutant mice generated by chemical mutagenesis using N-ethyl-nitrosourea [65]. The mdx<sup>5cv</sup> has a mutation at the 3′ end of the dystrophin gene, thus resulting in deficiency of the shorter isoforms. Absence of all dystrophin isoforms along with utrophin, however, does not worsen the dystrophic phenotype compared to the utrn<sup>−/−</sup>/mdx mouse [66].

Attempts have also been made to produce a dystrophin gene knockout mouse (mdx52). Araki et al. deleted exon 52 of dystrophin to produce a mouse with a similar phenotype to the mdx mouse [67].

**Table 3**

<table>
<thead>
<tr>
<th>Genotype (protein absent)</th>
<th>Life-span</th>
<th>Skeletal dystrophy</th>
<th>Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sgca&lt;sup&gt;−/−&lt;/sup&gt; (α-sarcoglycan)</td>
<td>&gt;1 yr</td>
<td>Moderate</td>
<td>None</td>
</tr>
<tr>
<td>Sgcb&lt;sup&gt;−/−&lt;/sup&gt; (β-sarcoglycan)</td>
<td>&gt;1 yr</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Sgcg&lt;sup&gt;−/−&lt;/sup&gt; (γ-sarcoglycan)</td>
<td>20 wks</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Sgcd&lt;sup&gt;−/−&lt;/sup&gt; (δ-sarcoglycan)</td>
<td>&gt;1 yr</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Sspn&lt;sup&gt;−/−&lt;/sup&gt; (sarcospan)</td>
<td>&gt;1 yr</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>DG&lt;sup&gt;−/−&lt;/sup&gt; (dyroglycan)</td>
<td>Embryonic lethal</td>
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<td>NA</td>
</tr>
<tr>
<td>DG chimeric (dyroglycan absent in skeletal and cardiac muscle)</td>
<td>&gt;1 yr</td>
<td>Moderate?</td>
<td>Severe</td>
</tr>
<tr>
<td>Myd (large)</td>
<td>Reduced</td>
<td>Moderate</td>
<td>None</td>
</tr>
<tr>
<td>Mdx&lt;sup&gt;−/−&lt;/sup&gt; (dystrophin)</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Mdx&lt;sup&gt;−/−&lt;/sup&gt; (dystrophin, Dp71, Dp116, Dp140, Dp260)</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Mdx&lt;sup&gt;−/−&lt;/sup&gt; (dystrophin, Dp140, Dp260)</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Mdx&lt;sup&gt;−/−&lt;/sup&gt; (dystrophin, Dp140, Dp260)</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Mdx52 (dystrophin, Dp140, Dp260)</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>None</td>
</tr>
<tr>
<td>Dp71&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt;6 months</td>
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<td>None</td>
</tr>
<tr>
<td>Mih/mdx (myocyte nuclear factor, Dystrophin)</td>
<td>~3 wks</td>
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<td>NT</td>
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<tr>
<td>MyoD/mdx (MyoD, dystrophin)</td>
<td>1 yr</td>
<td>Severe</td>
<td>Severe</td>
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<tr>
<td>nNOS/mdx</td>
<td>&gt;1 yr</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>nNOS/mdx</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Utrn&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Utrn&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Utrn&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Utrn&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Utrn&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Utrn&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt;1 yr</td>
<td>Mild/moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Dmd&lt;sup&gt;−/−&lt;/sup&gt; (dystrobrevin)</td>
<td>4–20 wks</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Adnb&lt;sup&gt;−/−&lt;/sup&gt; (dystrobrevin)</td>
<td>4–20 wks</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Adnb&lt;sup&gt;−/−&lt;/sup&gt; (dystrobrevin)</td>
<td>&gt;1 yr</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Utrn&lt;sup&gt;−/−&lt;/sup&gt;/mdx/abdn&lt;sup&gt;−/−&lt;/sup&gt; (utrophin, dystrophin, α-dystrobrevin)</td>
<td>8–10 months</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Utrn&lt;sup&gt;−/−&lt;/sup&gt;/mdx/abdn&lt;sup&gt;−/−&lt;/sup&gt; (utrophin, dystrophin, α-dystrobrevin)</td>
<td>3–11 wks</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>α1-syntrophin&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt;1 yr</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Cav-3&lt;sup&gt;−/−&lt;/sup&gt; (caveolin-3)</td>
<td>&gt;30 wks</td>
<td>Mild</td>
<td>None</td>
</tr>
</tbody>
</table>

NA, not applicable; NT, not tested. (For references, please see main text.)

**Syntrophin**

α1-syntrophin is strongly expressed at the sarcolemma and is a core protein of the DGC [7,37]. Yet, mice deficient in α1-syntrophin display no gross histological changes in the skeletal muscle and muscle contractile properties are not altered in these mice [68,69]. nNOS is misplaced from the sarcolemma of these mice and so is aquaporin-4, a mercurial-insensitive water-selective channel [70]. Aquaporin-4 is also absent in skeletal muscle of mdx mice [71]. Yet, the role of aquaporin-4 in the pathogenesis of muscular dystrophy is unclear as aquaporin-4-deficient mice maintain normal muscle function [72]. α1-syntrophin is also expressed abundantly at the neuromuscular junction, and recent studies reveal that absence of α1-syntrophin leads to structurally aberrant neuromuscular synapses deficient in utrophin [69].

**Dystrobrevin**

The best-studied functions of the DGC involve structural stabilization of the sarcolemma: mutations of several DGC components appear to cause muscular dystrophy by disassembling the complex and compromising the linkage between the extracellular matrix of the fibers to its cytoskeleton. Mice deficient in α-dystrobrevin maintain the expression of the DGC at the sarcolemma; yet, these mice develop a mild muscular dystrophy. Analysis of α-dystrobrevin mice revealed that muscular dystrophy might also develop as a result of impaired DGC-dependent signaling. The mechanism behind the disrupted signaling...
remains to be determined but nNOS may be involved. During exercise, nNOS activity is stimulated to produce cyclic GMP, which is necessary to maintain the blood flow in the active muscle. In electrically stimulated muscle of α-dystrobrevin deficient mice, cyclic GMP levels are not affected in agreement with the finding that nNOS is displaced from the muscle membrane [21]. Yet, loss of nNOS alone is unlikely to account for the dystrophy in α-dystrobrevin-deficient mice, as mice lacking nNOS are not dystrophic [73]. Moreover, the genetic loss of nNOS does not alter the pathogenesis of mdx mice [74]. However, recent studies suggest that at least part of the muscle degeneration observed in DMD patients may result from the reduced production of muscle-membrane-associated nNOS. This reduction may lead to improper control of the vasculature and eventual local muscle ischemia [75].

Caveolin-3
Caveolin-3 is a muscle-specific protein integrated in the caveolae, which are small invaginations of the plasma membrane. Mutations in the human caveolin-3 gene cause mild muscular dystrophy (LGMD 1C) [76]. Moreover, caveolin-3 has by immunoprecipitation experiments been shown to interact with dystrophin [77] but it is not an integral component of the DGC [78]. Very recently, caveolin-3-deficient mice were generated [79,80]. These mice exhibit very mild myopathic changes [79,80]. Interestingly, Lisanti and co-workers showed that caveolin-3 expression is required for correct targeting of the DGC to cholesterol-sphingolipid raft domains/caveolae in normal muscle fibers [80].

Animal models for dystroglycan deficiency
Dystroglycan was originally isolated from skeletal muscle but has since been shown to be expressed in a wide variety of tissues and is now considered to be the most broadly expressed DGC component [10,81]. Besides muscle, dystroglycan is expressed at high levels in developing and adult tissues, typically in cell types that adjoin basement membranes such as epithelial and neural tissue [82–84]. Early in vitro work demonstrated a role for dystroglycan in epithelial morphogenesis [82]. In 1997, the dystroglycan gene was disrupted in mouse [85]. Dystroglycan null embryos fail to progress beyond the early egg cylinder stage of development and are characterized by structural and functional perturbations of Reichert’s membrane, one of the earliest basement membranes that form in the rodent embryo. Subsequent work demonstrated a role for dystroglycan in the formation of the basement membrane of the embryoid body [84]. Because dystroglycan null embryos die early in development prior to gastrulation (i.e. long before any muscle has formed) it is not possible to analyze the consequences of dystroglycan deficiency in muscle. To overcome this, Carbonetto and co-workers generated chimeric mice, lacking dystroglycan in skeletal muscle [86]. Interestingly, Lisanti and co-workers showed that dystroglycan null embryos die early in development prior to gastrulation (i.e. long before any muscle has formed) it is not possible to analyze the consequences of dystroglycan deficiency in muscle. To overcome this, Carbonetto and co-workers generated chimeric mice, lacking dystroglycan in skeletal muscle [86]. Interestingly, these mice develop progressive muscle pathology with changes emblematic to muscular dystrophies in humans. In addition, many neuromuscular junctions are disrupted in these mice. Thus, dystroglycan is necessary for myofiber stability and synapse differentiation or stability. Surprisingly, the basement membrane in the chimeric mice is not grossly perturbed. Yet, the sarcoglycans and dystrophin are absent from the dystroglycan-deficient
muscle fibers suggesting that the sarcolemmal basement membrane interactions are weakened and/or disorganized.

It is becoming increasingly clear that posttranslational modifications of muscle cell proteins, in particular α-dystroglycan, are important for normal muscle function. Grewal et al. [87••] recently presented very intriguing data on the importance of correct glycosylation of α-dystroglycan. The myodystrophy mouse (myd) harbors a mutation in the glycosyltransferase, Large, which leads to altered glyco-sylation of α-dystroglycan (however, with no apparent shift in the molecular weight of α-dystroglycan) and mutant mice develop a progressive myopathy [87••]. Furthermore, muscle–eye–brain disease (MEB) is a type of congenital muscular dystrophy associated with loss-of-function mutations in the gene encoding a glycosyltransferase, POMGnT1 [88••]. POMGnT1 is a half-cysteine protein Disulfide-bridge (MEB) is a type of congenital muscular dystrophy associated with loss-of-function mutations in the gene encoding a glycosyltransferase, POMGnT1 [88••]. POMGnT1 is a glycosyltransferase that participates in the synthesis of O-mannosyl glycan, a modification that is rare in mammals but is present in α-dystroglycan. Kano et al. [89] recently reported a deficiency of α-dystroglycan, but not β-dystroglycan in MEB patients. A similar selective secondary deficiency of heavily glycosylated α-dystroglycan was also noted in Fukuyama congenital muscular dystrophy (FCMD; in which the gene encoding fukutin is affected) [90]. In summary, a growing body of evidence indicates that some muscular dystrophies may be caused by abnormal glyco-sylation of α-dystroglycan. The mechanistic basis for these disorders is yet to be determined.

**Animal models for laminin-2 deficiency**

In skeletal muscle, α-dystroglycan binds to the basement membrane protein laminin-2 (composed of laminin α2, β1 and γ1 chains) [24]. About 50% of the patients diagnosed with classical CMD show a primary deficiency of the laminin α2 chain and basement membrane perturbations [91]. Several mouse models for laminin-2 deficiency now exist, including the dy (dystrophy-muscularis) mouse, originally identified at the Jackson Laboratory [24,92,93], and an allelic mutant of the dy mouse, dy3 [94]. Neither of these mouse models exhibits a complete deficiency of laminin α2 chain. Yet, they both display a muscular dystrophy, although the muscular dystrophy in the dy3 mutants presents itself in a milder form compared to the dy mouse. Several laboratories have also generated null mutants for laminin α2 chain (dy3, dy3W) and all of these mouse models present a severe muscular dystrophy caused by the failure to form a laminin scaffold, which is necessary for basement membrane structure and for interactions with the DGC and integrins [95,96]. Interestingly, a mini agrin gene, which retained high-affinity binding sites for the laminins that are upregulated in dy3W mice (laminin α4 and laminin α5 chains) and α-dystroglycan compensated for the loss of laminin α2 chain [97••]. This suggests that even a non-homologous high-affinity link between dystroglycan and the extracellular matrix is sufficient to prevent muscular dystrophy.

**Animal models for integrin deficiency**

Laminins also bind integrins, which are a large family of heterodimeric transmembrane cell surface receptors that are important for normal muscle function. Grewal et al. [87••] recently presented very intriguing data on the importance of correct glycosylation of α-dystroglycan. The myodystrophy mouse (myd) harbors a mutation in the glycosyltransferase, Large, which leads to altered glyco-sylation of α-dystroglycan (however, with no apparent shift in the molecular weight of α-dystroglycan) and mutant mice develop a progressive myopathy [87••]. Furthermore, muscle–eye–brain disease (MEB) is a type of congenital muscular dystrophy associated with loss-of-function mutations in the gene encoding a glycosyltransferase, POMGnT1 [88••]. POMGnT1 is a glycosyltransferase that participates in the synthesis of O-mannosyl glycan, a modification that is rare in mammals but is present in α-dystroglycan. Kano et al. [89] recently reported a deficiency of α-dystroglycan, but not β-dystroglycan in MEB patients. A similar selective secondary deficiency of heavily glycosylated α-dystroglycan was also noted in Fukuyama congenital muscular dystrophy (FCMD; in which the gene encoding fukutin is affected) [90]. In summary, a growing body of evidence indicates that some muscular dystrophies may be caused by abnormal glyco-sylation of α-dystroglycan. The mechanistic basis for these disorders is yet to be determined.

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**Animal models for integrin deficiency**

Laminins also bind integrins, which are a large family of heterodimeric transmembrane cell surface receptors that function in a wide variety of cell interactions [98]. In skeletal muscle, the α7β1 integrin is the predominant integrin that binds laminin-2 [99]. It is possible that the functions of the DGC and the integrin α7 complex in skeletal muscle to some extent overlap. Mice lacking integrin α7 display a mild myopathy [100] and, interestingly, mice lacking both integrin α7 and dystrophin develop a severe dystrophy and die between 3–4 weeks of age (U Mayer, unpublished data). The fact that the expression of integrin α7 transcript and protein is increased in mdx mice and in DMD patients further suggests that the integrin α7β1 may compensate for the absence of the DGC [101,102]. Indeed, transgenic expression of the α7β1 integrin reduces muscular dystrophy and restores viability in the dystrophic utrn+/−/mdx mouse [103].

**Figure 3**

Schematic diagram of sarcoglycan complexes in muscle. (a) Mouse skeletal muscle was stained with β-sarcoglycan antibodies. 

(b) Normal skeletal muscle contains two sarcoglycan complexes: an α-sarcoglycan and an ε-sarcoglycan containing complex. The former is composed of α, β, and γ-sarcoglycan whereas the latter is composed of at least ε- and δ-sarcoglycan and perhaps γ-sarcoglycan (denoted by a broken line). Note that only the sarcoglycan complexes (and not the entire DGC) are illustrated.

(c) Mouse cardiac muscle was stained with β-sarcoglycan antibodies.

(d) Two sarcoglycan complexes are also present within cardiac muscle. (e) Pulmonary artery is positively stained with β-sarcoglycan antibodies. (f) The smooth muscle sarcoglycan complex is composed of ε, β, γ and δ-sarcoglycan.
Although α7β1 integrin is the predominant integrin that binds laminin-2 in skeletal muscle, other integrins are important for normal muscle function too. Mice chimeric for the expression of integrin α5 (receptor for fibronectin) also develop a myopathy [104].

In summary, these data suggest that both the DGC and integrins are involved in anchoring the muscle fiber to its extracellular matrix and that disruption of this anchorage results in muscle instability and subsequently cell death.

**Animal models for sarcoglycan–sarcospan deficiency**

The sarcoglycan complex is a group of single-pass transmembrane proteins (α-, β-, γ- and δ-sarcoglycan) that is tightly associated with sarcospan to form a subcomplex within the DGC [105]. Although the exact function of the sarcoglycan–sarcospan complex is not known, it is well established that mutations in any of α-, β-, γ- and δ-sarcoglycan genes result in distinct forms of muscular dystrophy now collectively called sarcoglycanopathies [11,14–18,32]. A primary mutation in any one of these genes may lead to either total or partial loss of that sarcoglycan as well as a secondary deficiency of the other sarcoglycans [106]. Furthermore, sarcospan expression is dependent on proper expression of the sarcoglycans [58,105,107]. To date, however, no human mutations have been found in the sarcospan gene, nor have any unclassified muscular dystrophies been mapped to the chromosomal location of sarcospan [107]. Moreover, sarcospan-deficient mice maintain their sarcolemmal expression of DGC and maintain normal muscle function [108].

The sarcoglycans are primarily expressed in muscle. α-, β-, γ-, and δ-sarcoglycan are, along with sarcospan, expressed in skeletal and cardiac muscle [109]. In smooth muscle, on the other hand, a unique sarcoglycan–sarcospan complex is expressed. The smooth muscle sarcoglycan complex is composed of ε-sarcoglycan (an α-sarcoglycan homologue) instead of α-sarcoglycan, along with β-sarcoglycan, γ-sarcoglycan and δ-sarcoglycan [81,109,110*]. The sarcoglycan–sarcospan complex is in smooth muscle also associated with dystroglycan. However, dystroglycan in smooth muscle is differentially glycosylated compared to dystroglycan in skeletal muscle [109].

Recent data from several laboratories, including ours, have demonstrated that proper expression of the sarcoglycans in skeletal muscle is a necessity for normal skeletal muscle function [58,111–114,115**]. Furthermore, we have recently demonstrated that proper expression of the sarcoglycans in smooth muscle is also of great importance for normal skeletal and cardiac muscle function [112,115**].

Mice deficient in α-sarcoglycan (Sgca null mice), which is exclusively expressed in striated muscle, develop a progressive muscular dystrophy and a concomitant deficiency in β-, γ- and δ-sarcoglycan along with sarcospan in skeletal muscle. Furthermore, α-dystroglycan is greatly destabilized at the sarcolemma, indicating that membrane expression of the sarcoglycans is a prerequisite for membrane targeting and stabilization of α-dystroglycan. The sarcoglycan–sarcospan complex is also significantly reduced in cardiac muscle of Sgca null mice. Yet, these mice do not develop cardiomyopathy [58]. The reason for this became clear when β- and δ-sarcoglycan-deficient mice were generated and analyzed in our laboratory [112,115**]. Mice deficient in β- and δ-sarcoglycan (Sgcb null mice and Sgcd null mice, respectively) that are expressed in both striated and smooth muscle also develop a progressive muscular dystrophy, which seems to be more severe than in Sgca null mice. Large, focal areas of necrosis/fibrosis are present in skeletal muscle of Sgcb and Sgcd null mice, a phenomenon that is not detected in Sgca null mice. Both Sgcb and Sgcd null mice also develop cardiomyopathy and morphologically this is recognized by extensive areas of necrosis/fibrosis in the hearts. Additionally, the serum levels for cardiac-specific troponin I are elevated in these mice in agreement with the presence of acute myocardial necrosis that precedes the formation of fibrotic lesions [112,115**].

Furthermore, deficiency of β- and δ-sarcoglycan leads to perturbed expression of the entire sarcoglycan–sarcospan and dystroglycan complexes not only in striated muscle but also in vascular smooth muscle. The loss of the sarcoglycan–sarcospan complex in smooth muscle and the presence of the focal areas of necrosis in skeletal and cardiac muscle prompted us to analyze the blood vessels more closely in Sgcb and Sgcd null mice. Using the Microfil perfusion technique, we found vascular irregularities in the form of arterial constrictions in both heart and skeletal muscle and also in the kidneys of Sgcb and Sgcd null mice ([112,115**]; M Durbeej, KP Campbell, unpublished data) (see Figure 2). Importantly, the disturbance of the vasculature precedes the onset of ischemic-like lesions. Moreover, no vascular perturbations are present in Sgca null mice. α-sarcoglycan is not expressed in smooth muscle — the smooth muscle sarcoglycan is thus intact in Sgca null mice. Still, Sgca null mice are dystrophic. Together, these data suggest that muscle degeneration does not cause the vascular phenotype. Instead, loss of the sarcoglycan–sarcospan complex in smooth muscle of blood vessels results in vascular irregularities that aggravate skeletal pathology and initiate heart pathology as a result of diminished delivery of oxygen and nutrients [112,113**,116**].

Biochemical analysis of sarcoglycan deficient mice revealed the presence of a new sarcoglycan complex in skeletal and cardiac muscle ([114,115**]; M Durbeej, KP Campbell, unpublished data). This additional sarcoglycan complex is composed of at least ε-, β-, and δ-sarcoglycan, but neither dystrophin or utrophin [115**] (Figure 3). Thus, β- and δ-sarcoglycan mutations, but not α-sarcoglycan mutations, affect the expression of this complex, which is subsequently absent in Sgcb and Sgcd null mice but not Sgca null mice. Hence, loss of the ε-sarcoglycan complex
may also contribute to the more severe pathology seen in Sgcb and Sgcd null mice. Whether γ-sarcoglycan is part of the ε-sarcoglycan complex is not clear. ε-sarcoglycan expression remains in γ-sarcoglycan-deficient mice [111]. However, immunoprecipitation experiments indicate that γ-sarcoglycan is indeed part of the ε-sarcoglycan complex [114]. Clearly, more studies are needed to clarify this discrepancy.

In summary, a complex pathogenetic mechanism for the development of LGMD 2E and F can be postulated. Deficiency of β- and δ-sarcoglycan causes loss of the sarcoglycan-sarcospan and dystroglycan complexes as well as loss of the ε-sarcoglycan-containing complex in striated muscle. Since the linkage between the extracellular matrix and the muscle cell is perturbed, the skeletal and cardiac muscle membranes become unstable. Thus, the muscle cells may be more prone to ischemic damage that develops as a consequence of the absent smooth muscle sarcoglycan complex.

Although α-, β-, γ- and δ-sarcoglycans are part of the same complex, the individual sarcoglycans may exhibit different functional roles. Several lines of evidence support this idea. First, ecto-ATPase activity has been noted for α-sarcoglycan, indicating that α-sarcoglycan might function in controlling the ATP concentration at the surface of the muscle cell [117]. Second, mice deficient for γ-sarcoglycan exhibit a severe muscular dystrophy and cardiomyopathy [111]. Without γ-sarcoglycan, β- and δ-sarcoglycan are unstable at the muscle membrane and α-sarcoglycan is severely reduced. The expression of dystroglycan, however, is not altered and thus the link between the extracellular matrix and the intracellular cytoskeleton appears unaffected. Moreover, γ-sarcoglycan-deficient muscle show normal resistance to mechanical strain, normal peak isometric and tetanic force generation and no evidence for contraction-induced injury after exercise [118]. Thus, a nonmechanical mechanism (perhaps signaling) may be responsible for γ-sarcoglycan-deficient muscular dystrophy. These results are in sharp contrast to muscles of Sgca, Sgcb and Sgcd null mice, which show abnormal resistance to stretch, and a decrease in specific force generation ([158,112]; M Durbeej, KP Campbell, unpublished data).

Conclusions

Animal models lacking each component of the DGC have provided many new insights into the development of muscular dystrophy. Specifically, we have learned that muscular dystrophy can develop when DGC core components such as sarcoglycans, dystroglycan and dystrobrevins are missing from the skeletal muscle. In addition, muscular dystrophy can also develop when laminin-2 and integrins are absent. More importantly, analysis of these mouse models has unraveled novel pathogenetic mechanisms for the development of muscular dystrophy. For example, perturbation of vascular function together with the disruption of the ε-sarcoglycan complex contribute to the increased severity of mouse models of LGMD type 2E and F. Furthermore, these animal models will be tremendously valuable tools for testing novel therapeutic approaches. In fact, the feasibility of sarcoglycan gene transfer for sarcoglycanopathies has already been investigated using some of the sarcoglycan-deficient mice. These studies demonstrate that mutations in individual sarcoglycan components can be corrected in vivo ([119•,120•]; M Durbeej, KP Campbell, unpublished data). Moreover, the mouse models will be of immense benefit for evaluating possible drug therapies for muscular dystrophy and cardiomyopathy. For example, nicorandil, a vascular smooth muscle relaxant, prevents the acute onset of myocardial necrosis in Sgcd null mice [112]. Furthermore, recent studies in our laboratory suggest that verapamil, a pharmacological agent with vasodilator properties, successfully prevents cardiomyopathy in sarcoglycan-deficient mice by abolishing the vascular dysfunction [116••]. Taken together, the successful treatment of cardiomyopathy using agents with clinical relevance in mouse models lacking the smooth muscle sarcoglycan–sarcospan complex connotes that efforts toward drug therapies can be of tremendous benefit preventing certain forms of hereditary cardiomyopathy and perhaps muscular dystrophy.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest


Muscular dystrophies involving the dystrophin–glycoprotein complex Durbeej and Campbell 359


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110. Barresi R, Moore SA, Stolle CA, Mendell JR, Campbell KP: Expression of γ-sarcoglycan in smooth muscle and its interaction with the smooth muscle sarcoglycan-sarcospan complex. J Biol Chem 2000, 275:38554-38560. The expression pattern of γ-sarcoglycan in smooth muscle is biochemically and genetically evaluated in this paper as it had been unclear whether γ-sarcoglycan is expressed in smooth muscle. The authors provide convincing evidence that γ-sarcoglycan is a component of the smooth muscle sarcoglycan complex.
Muscular dystrophies involving the dystrophin–glycoprotein complex Durbeej and Campbell 361


This paper shows that early adenovirus-mediated gene transfer effectively prevents muscular dystrophy in α-sarcoglycan deficient mice. One single injection of a first generation adenovirus into the skeletal muscle of neonate mice led to sustained expression of α-sarcoglycan at the sarcolemma of transduced fibers for at least 7 months.


The authors demonstrate that injections of a recombinant adeno-associated virus – in which human α-sarcoglycan is driven by a muscle creatine kinase promoter – into skeletal muscle of α-sarcoglycan-deficient mice result in an overall improvement of the histological pattern of dystrophy. However, the authors underscore the need for intervention early in the time course of the disease process.


