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INVITED REVIEW

Cell–matrix interactions in muscle disease

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Abstract

The extracellular matrix (ECM) provides a solid scaffold and signals to cells through ECM receptors. The cell–matrix interactions are crucial for normal biological processes and when disrupted they may lead to pathological processes. In particular, the biological importance of ECM–cell membrane–cytoskeleton interactions in skeletal muscle is accentuated by the number of inherited muscle diseases caused by mutations in proteins conferring these interactions. In this review we introduce laminins, collagens, dystroglycan, integrins, dystrophin and sarcoglycans. Mutations in corresponding genes cause various forms of muscular dystrophy. The muscle disorders are presented as well as advances toward the development of treatment.

Keywords: muscle; extracellular matrix; membrane; cytoskeleton; disease; muscular dystrophy

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Introduction

The extracellular matrix (ECM) is a dynamic structure that provides support and anchorage for cells, segregates tissues from one another and initiates signal transduction pathways. The ECM is composed primarily of glycoproteins, collagens and proteoglycans that are secreted and assembled locally into an organized network to which cells adhere via cell surface receptors. An ECM is already present in the mammalian embryo from the two-cell stage and is a component of the environment of all cell types, although the composition of the ECM and the spatial relationship between cells and the ECM differ between tissues. The ECM includes the interstitial matrix and the basement membrane.

The interstitial matrix is present between cells, while the basement membrane is a thin sheet-like deposition of ECM that surrounds cells (eg muscle cells) or underlies cells (eg epithelial cells) [1,2]. The major components of the basement membranes are laminins, collagen type IV, nidogens and the heparan sulphate proteoglycan perlecan. Laminins and collagen type IV form independent networks that are connected by nidogens and perlecan and the basement membrane is associated with cells through interactions with cell surface receptors (eg integrins and dystroglycan). Hence, a major role of the basement membrane is to provide a solid scaffold for the cells and to separate them from the surrounding interstitial matrix. Apart from providing tissue structure, the basement membrane is also crucial for survival and differentiation of cells. Furthermore, it represents an important barrier that limits bacterial/viral infections or malignant cell infiltration into tissues [3]. Consequently, altered basement membranes are responsible for various human diseases. Particularly, in skeletal muscle, mutations in genes encoding ECM proteins and their receptors are accountable for several types of muscular dystrophy and, in particular, congenital muscular dystrophy [4].

Congenital muscular dystrophy forms a heterogeneous group of progressive genetic diseases that are mostly, but not exclusively, inherited in an autosomal recessive manner. The clinical symptoms are present from birth or during the first months of life and include neonatal hypotonia, muscle weakness, delayed motor milestones and joint contractions. Some forms are also associated with central nervous system or peripheral nerve defects. The main morphological features, observed in muscle biopsies, are degeneration–regeneration processes (evidenced by the presence of fibres with centrally located nuclei) and fibrosis infiltration within the muscle tissue [5]. Phenotypical variability is present in this group of diseases and ranges from severe and lethal forms to milder types compatible with a normal life span. Depending on the genetic defect, it is possible to distinguish four forms of congenital muscular dystrophy linked to ECM or matrix receptor defects; two associated with mutations in laminin α2 chain and collagen VI (congenital muscular dystrophy type 1A and Ullrich/Bethlem congenital muscular dystrophy, respectively) and two correlated with defective laminin α2 chain receptors (dystroglycanopathies and integrin α7 deficient congenital myopathy, respectively) [6–16].

Moreover, putative heterozygous mutations in collagen IV α1 chain were recently described in patients affected by muscle–eye–brain disease and Walker–Warburg syndrome [17]. Previously, these two disorders were mainly attributed to alterations in glycosylation of α-dystroglycan [18].

α-Dystroglycan is a member of the dystrophin–glycoprotein complex (DGC), a large complex of membrane-associated proteins that is critical for the integrity of skeletal muscle fibres. The DGC provides a link between the ECM and the cytoskeleton and is believed to protect the muscle fibre from contraction-induced damage [19,20]. The DGC is further composed of β-dystroglycan, dystrophin, the sarcoglycans (α, β, γ and δ), sarcospan, the syntrophins (α1, β1) and α-dystrobrevin [21–24]. Notably, mutations in many of its components cause impaired ECM–cell membrane–cytoskeletal interactions, resulting in severe skeletal muscle disease. Particularly, human mutations in dystrophin-, sarcoglycan- and dystroglycan-encoding genes are associated with Duchenne and its allelic variant Becker muscular dystrophy; limb-girdle muscular dystrophy types 2C–F and primary dystroglycanopathy, respectively [15,25–31]. Duchenne muscular dystrophy (DMD), which is inherited in an X-linked recessive pattern, is the most common type of muscular dystrophy, affecting around 1 in 3500 boys. Unlike congenital muscular dystrophies that are manifested at birth, patients with DMD have a childhood onset phenotype, while the age of onset in patients with limb-girdle muscular dystrophy varies from childhood to adulthood.

In summary, it is evident that the ECM–cell membrane–cytoskeleton linkage is crucial for maintenance of skeletal muscle function. In this review, we describe the structure and functions of laminins, collagens, laminin receptors and dystroglycan-associated proteins. We also discuss the molecular pathogenesis of the muscular dystrophies that are caused by primary genetic or secondary functional defects in these molecules as well as how these disorders may be therapeutically targeted.

Laminins

Structure and function

Laminins comprise a group of high molecular weight glycoproteins (400–900 kDa), abundant in the basement membrane [3,32]. Mature laminin proteins are cross- or T-shaped, composed by one α, one β and one γ chain that associate to form a heterotrimeric molecule (Figure 1). Up to now, five α, three β and three γ chains have been characterized, and they combine to form at least 15 different laminin isoforms [33,34]. The laminin heterotrimers are assembled inside the cell, but extracellular maturation by proteolytic cleavage may occur in various chains [33]. All laminin chains share a common domain structure, with a number of globular and rod-like domains. In most laminins, but not all, the short arm is formed by the N-terminal extremity (LN domain) of α, β and γ chains, followed by a variable number of globular domains separated by rod-like spacers. The long arm consists of the three chains joined in a coiled-coil domain and the C-terminal extremity of the α chain, which is composed of five homologous globular domains (LG domains 1–5). Laminin polymerization occurs through connections between the LN domains in each chain and is dependent on the presence of the laminin receptors dystroglycan and integrin [35,36]. The laminin LG domains are engaged in binding dystroglycan and integrin and these interactions are crucial for basement membrane formation, cell differentiation and cell survival [37]. Finally, laminins contain binding domains for other ECM macromolecules. For instance, a single domain within the laminin γ1 and γ3 chains, respectively, binds nidogens [38–41] and perlecan also binds laminins [42].

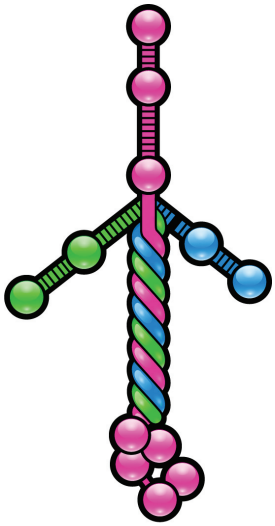

Figure 1. Representative model of a cruciform laminin molecule. The laminins are composed of three polypeptide chains; α (in pink), β (in green) and γ (in blue), which interact forming a coiled-coil domain. The globular domain at the N-terminal of each chain is involved in network formation. The C-terminal end of the α chain is composed of five laminin globular domains that bind dystroglycan and integrins (as well as heparin, sulphatides, perlecan and fibulins).

Congenital muscular dystrophy with laminin α2 chain deficiency

In skeletal muscle, the major laminin isoform is composed by α2, β1 and γ1 chains [43], making up laminin-211 (formerly called merosin). Laminin α2 chain is encoded by the *LAMA2* gene and homozygous mutations in this gene are responsible for congenital muscular dystrophy type 1A (MDC1A) (MIM ID #607 855) [14]. It represents approximately 50% of all congenital muscular dystrophies [44]. This disorder is characterized by severe muscle weakness, hypotonia, joint contractures, dysmyelinating peripheral neuropathy and brain defects [45]. Missense, nonsense, splice-site mutations and deletions

in the whole *LAMA2* gene have been reported [46] and are summarized in the *LAMA2* gene database (www.dmd.nl/LAMA2_seqvar.html). Depending on the type of mutation, complete or partial absence of laminin α2 chain can be observed in skeletal muscle. Except for rare cases, patients displaying complete laminin-211 deficiency generally appear to develop a homogenous severe phenotype with an onset of muscle weakness within the 6 first months of life, incapacity to acquire independent ambulation, joint contractures and white matter abnormalities [47–49]. In this group, the mutations are localized throughout the whole gene, but four hot-spots (in exons 14, 25, 26 and 27) represent 55% of the mutations [49]. In the group of patients with partial deficiency, the majority of mutations are splice-site and frameshift mutations, but missense and nonsense mutations can also occur [50,51]. They are associated with a more heterogeneous course of the disease with either a severe or a milder phenotype [49,52].

How does the absence/reduction of laminin α2 chain lead to muscle degeneration? This is not fully understood. However, typical features of MDC1A include disrupted basement membranes [53] and increased apoptosis [54,55]. Hence, the laminin α2 chain might mediate survival signals through both integrin α7β1 and dystroglycan [56,57], and it has been proposed that laminin α2 chain binding to α-dystroglycan strengthens the cell membrane integrity by anchoring the basement membrane to the sarcolemma [58]. It was also recently demonstrated that enhanced activity of the proteasome and the autophagic process, respectively, is pathogenic in laminin α2 chain-deficient muscle [59,60]. Still very little is known regarding the laminin α2 chain-induced signal transduction pathways leading to increased apoptosis and enhanced protein degradation. Deciphering such pathways remains essential in order to further clarify the details of laminin α2 chain function.

Collagen IV

Structure and function

Collagen IV is also a ubiquitous protein of the basement membrane. Its primary structure is composed of 90% of Gly–Xaa–Yaa repeats, forming a collagenous domain that allows the assembly of a triple-helix structure. In particular, the glycine residues are crucial for the triple-helix formation and many human mutations affect the glycine residues. Collagen IV also has a short non-helical N-terminal domain (7S) and a highly conserved C-terminal globular domain (NC1) (Figure 2). After synthesis, NC1 domain interactions initiate the formation of three different trimers, encoded from six distinct genes (*COL4A1–6*); the α1α1α2 trimer (which is ubiquitously expressed) and the α3α4α5 and α5α5α6 trimers (with a more restricted expression pattern). Unlike fibril-forming collagens, collagen IV forms a network. In the extracellular space, the type

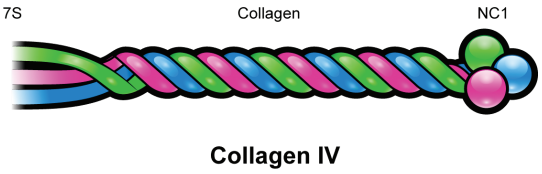

Figure 2. Schematic diagram of a collagen IV protomer. Collagen IV is composed of three polypeptide chains (different combinations of α1–α6 chains). The central collagen domain is flanked by the N-terminal 7S domain and the C-terminal non-collagenous domain 1 (NC1). Through complex interactions, the heterotrimeric collagen IV forms a network. Integrin binding sites are located in the NC1 domain and in a domain located 100 nm away from the N-terminal.

IV collagen network is formed by complex interactions involving the formation of NC1 hexamers, 7S domain heterotrimers and lateral interactions between the helical domains [61,62]. Similarly to laminins, the collagen IV network interacts with the cell surface, mainly through β1 chain-containing integrins and several non-integrin receptors [63–68]. In addition, there are several binding sites for laminin in the collagen IV triple helix, as well as binding sites for heparan sulphate proteoglycans and nidogens [69,70].

Congenital muscular dystrophy due to collagen IVα1 mutations

Until recently, no mutation in the six genes encoding the collagen IV chains had been associated with a muscle disorder. Instead, mutations found in collagen IV-encoding genes have been demonstrated to be linked to several other diseases, and in particular kidney disorders [60]. Also, mutations in *COL4A1* are coupled to rare genetic diseases. In humans and mice with mutated *COL4A1*, a phenotypic variability is often observed but in general the abnormalities include cerebrovascular disease, ocular and renal defects [71–88]. Interestingly, it has now been described that the congenital muscular dystrophies muscle–eye–brain disease and Walker–Warburg syndrome could be linked to heterozygous mutations in the collagenous domain of *COL4A1* [17]. Also, heterozygous *Col4a1* mutant mice display ocular dysgenesis, neuronal localization defects and myopathy, all characteristics of muscle–eye–brain disease and Walker–Warburg syndrome. The molecular mechanism triggering the disease is apparently independent of α-dystroglycan glycosylation and instead collagen IV may not be properly secreted, leading to less deposition of collagen IV in the basement membrane and hence ruptured basement membranes [17].

Collagen VI

Structure and function

Collagen VI, a beaded filament-forming collagen, is an abundant interstitial matrix protein that is closely associated with basement membranes in many organs.

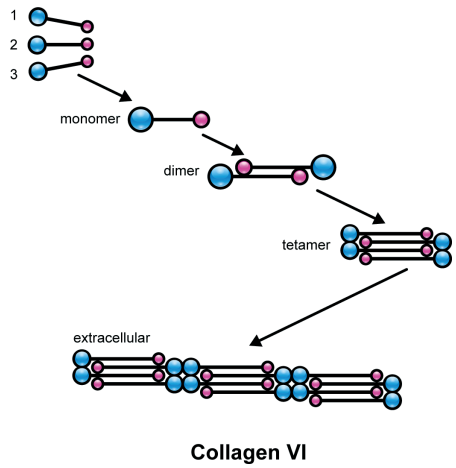

Figure 3. Schematic description of collagen VI assembly. Inside the cell, heterotrimeric monomers first assemble into dimers and then tetramers that are secreted. Extracellularly, the tetramers compile into long molecular chains (microfibrils).

For example, in skeletal muscle, collagen VI is mainly produced by the fibroblasts [89] but is involved in anchoring the basement membrane to the adjacent connective tissue [90,91]. The complex collagen VI network interacts with numerous proteins and has a crucial role in cell proliferation and survival [92,93]. Collagen VI is composed by three major polypeptidic chains (α1, α2 and α3) encoded by three different genes, *COL6A1, COL6A2* and *COL6A3*, respectively. Also, three additional genes have been described, encoding α4, α5 and α6 chains with a more restricted expression pattern [94]. Each chain has an N-terminal and a C-terminal large globular domain, which are connected by a central short triple-helical domain of Gly–Xaa–Yaa amino acid repeat sequences [95]. Before secretion into the extracellular space, the three chains associate to form a trimer, which further assembles into disulphide-bonded anti-parallel dimers and then tetramers [96]. After secretion into the extracellular space, the tetrameric molecules form the microfibrillar network by an end-to-end association with overlapping N-terminal domains, giving rise to a typical beaded appearance with a periodicity of 105 nm (Figure 3) [97]. Collagen VI microfibrils interact with several components of the basement membrane (eg collagen IV and perlecan) [98,99] and with the cell surface through β1 chain containing integrins [100]. Interactions with other constituents of ECM, such as fibronectin [101], biglycan and decorin [102,103], have also been described.

Ullrich congenital muscular dystrophy and Bethlem myopathy

Mutations in *COL6A1, COL6A2* and *COL6A3* genes are associated with Ullrich congenital muscular dystrophy (UCMD, MIM ID No. 254 090) and Bethlem myopathy (MIM ID No. 158 810) [16]. UCMD represents the second most frequent form of congenital muscular dystrophy after MDC1A. Initially, UCMD was believed to be recessively inherited while dominant mutations were considered to cause Bethlem myopathy. However, an increasing number of heterozygous and severely affected carriers have been reported. Now these two entities are considered as two extremes of the same clinical spectrum. Classical UCMD is characterized by a severe generalized early-onset muscle weakness, slowly progressive proximal limb contractures, distal hyperlaxity, rigid spine and severe respiratory deficiency [9,11]. UCMD patients have normal IQ and MRI images show a normal development of the brain. The patients affected by classical Bethlem myopathy develop a milder, slowly progressive or static generalized muscle weakness and joints contractures [104]. A high level of heterogeneity regarding the phenotype and expression levels of collagen VI is observed in this disease and even within the same family. A growing number of *de novo* mutations have been reported, suggesting that peculiar regions of the genes are susceptible to neomutations [10,105]. Numerous polymorphisms in the *COL6A* genes could also contribute to the phenotypic variability. Because of this heterogeneity, several studies aimed at delineating genotype–phenotype correlations have been carried out. By analysing collagen VI expression and secretion in patient fibroblasts and muscle biopsies, a connection between expression and clinical severity was recently demonstrated [10–12]. Yet, this correlation was not demonstrated in other reports [106,107]. Nevertheless, the use of quantitative RT–PCR was lately proposed to accelerate the identification of the gene defect, since reduced transcript levels are associated with all types of mutations in *COL6A* genes [10].

By studies of mice with defective collagen VI secretion (and humans with UCMD or Bethlem myopathy) it has been proposed that the molecular pathogenesis of collagen VI-deficient muscular dystrophy involves latent mitochondrial dysfunction accompanied by ultrastructural alterations of mitochondria and the sarcoplasmic reticulum and spontaneous apoptosis of muscle fibres [10,91]. Moreover, it was recently demonstrated that the accumulation of abnormal mitochondria and sarcoplasmic reticulum is caused by defective autophagy [108].However, it remains to be established how absence of an interstitial matrix protein can lead to muscle cell apoptosis, and therefore the identification of collagen VI muscle cell surface receptors may be an interesting task.

Dystroglycan

Structure and function

Dystroglycan is a widely expressed member of the DGC, involved in connecting the ECM with the intracellular cytoskeleton. Dystroglycan is encoded by the *DAG1* gene and undergoes major post-translational modifications, producing the highly glycosylated extracellular peripheral membrane protein α-dystroglycan

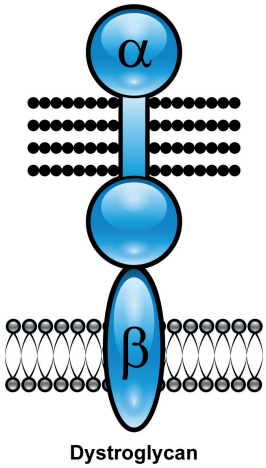

Figure 4. Schematic diagram of dystroglycan. The dystroglycan complex is composed of α-dystroglycan, which contains numerous *O*-linked oligosaccharides and β-dystroglycan. α-Dystroglycan binds laminin in the basement membrane and β-dystroglycan binds to the intracellularly located protein dystrophin.

and the transmembrane protein β-dystroglycan (Figure 4) [8,109]. Intracellularly, the cytoplasmic domain of β-dystroglycan links the C-terminal domain of dystrophin that interacts with the actin cytoskeleton. Extracellularly, β-dystroglycan binds α-dystroglycan, which in turn binds to laminin-211 [19], agrin [110] and perlecan [111] in the muscle basement membrane. At the synapse, α-dystroglycan also binds neurexin and pikachurin [112,113]. α-Dystroglycan contains a globular N-terminal and a C-terminal domain separated by a central mucin domain [114] rich in serine and threonine amino acids with attached complex *O*-linked glycans (eg *O*-mannosyl glycans). α-Dystroglycan is glycosylated by several putative and known glycosyltransferases and the presence of the oligosaccharides is crucial for the normal function of α-dystroglycan as a membrane receptor [7,8]. In particular, the ability to bind laminins and other ligands requires phosphorylation of *O*-mannosyl glycans, which is mediated by the glycosyltransferase LARGE [115] that interacts with the N-terminal domain of α-dystroglycan [116]. Furthermore, following functional glycosylation of α-dystroglycan, the N-terminal domain is proteolytically processed by the proprotein convertase furin [116,117].

Dystroglycanopathies

Congenital muscular dystrophies linked to abnormalities in the glycosylation of α-dystroglycan are commonly denominated dystroglycanopathies. This group of diseases could either be due to a primary mutation in the *DAG1* gene (primary dystroglycanopathy) or mainly due to mutations in genes encoding glycosyltransferases involved in the *O*-mannosyl-linked glycosylation of α-dystroglycan (secondary dystroglycanopathies). Recently, the first primary dystroglycanopathy was described. A missense mutation was discovered in a patient originally diagnosed with a mild form of limb-girdle muscular dystrophy with severe cognitive impairment. Interestingly, a mouse model harbouring the same mutation recapitulated the phenotype and it was further demonstrated that the missense mutation interferes with LARGE-mediated glycosylation of α-dystroglycan, resulting in a lower binding to laminin [15]. Secondary dystroglycanopathies represent the prominent cases of dystroglycanopathies and are autosomal recessive congenital muscular dystrophies caused by mutations in protein *O*-mannosyltransferase 1 and 2 (*POMT1, POMT2*), protein *O*-mannose β1,2-N-acetylglucosaminyltransferase 1 (*POMGnT*), fukutin-related protein (*FKRP*), fukutin and LARGE genes [8,118–125]. The resulting diseases are Walker–Warburg syndrome, muscle–eye–brain disease, congenital muscular dystrophy type 1C, Fukuyama-type congenital muscular dystrophy, congenital muscular dystrophy type 1D and limb-girdle muscular dystrophy type 2I, respectively. The clinical hallmarks of these disorders at the severe end of the spectrum include a characteristic combination of brain malformations, as well as eye defects or high myopia, but the spectrum extends from patients with mental retardation with normal brain structure to presentations of pure muscular dystrophy with normal cognition.

For all dystroglycanopathies, the common molecular feature involves abnormal glycosylation of α-dystroglycan, although a strong correlation between reduced glycosylated α-dystroglycan and clinical course may not be evident [126]. Hypoglycosylated α-dystroglycan in skeletal muscle and brain displays reduced capacity to bind its ECM ligands and consequently basement membrane deposition is defective [115,127]. However, in order to further understand the pathogenesis of dystroglycanopathies, it will be important to determine the exact glycan composition in normal and diseased skeletal muscle (as well as in other tissues) and to further determine the role of glycans in ligand binding.

Integrins

Structure and function

Integrins are a large family of surface receptors that also bridge the ECM to the intracellular cytoskeleton. Moreover, they are signalling receptors involved in both outside-in and inside-out signalling. Integrins consist of two non-covalently-associated subunits, α and β (Figure 5). Even if not genetically related to each other, the two subunits share a common structure. They display a large modular extracellular domain followed by a hydrophobic transmembrane α-helix and a relatively short C-terminal domain that points to the cytosol. This C-terminal domain lacks actin binding sites and enzymatic activities and consequently integrin signals are transduced through associated proteins, such as talin and integrin-linked kinase. At least 24 different receptors could be formed depending on the

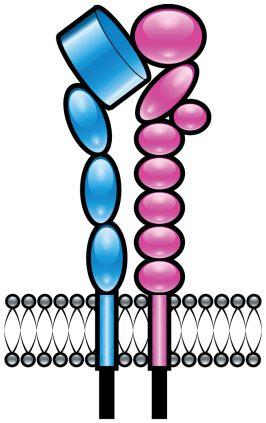

Figure 5. Representative model of an integrin. The α subunit (blue) consists of a β-propeller (top), a thigh domain, calf-1 and calf-2 domains, a transmembrane domain and a short cytoplasmic domain. The β subunit is composed of a βA domain (top), a hybrid domain, a plexin–semaphorin–integrin domain, four epidermal growth factor-like repeats, a β-tail domain, a transmembrane domain and a short cytoplasmic domain. The β-propeller and the βA domain are engaged in ligand binding.

combination of the 18α and 8β existing subunits [128,129]. Integrin α7β1 is the main integrin isoform expressed in striated muscle [130]. Several alternatively spliced isoforms of α7 and β1 chains have been described and some are differentially expressed during muscle development and regeneration [131]. In skeletal muscle, α7β1 integrin interacts mainly with laminin-211 but it can also bind other laminin isoforms [132,133]. Hence, the laminin-211–integrin α7β1 interaction creates an additional important link between the ECM and the cytoskeleton in skeletal muscle [134]. A functional redundancy may exist between integrin α7β1 and the DGC [135,136] and both integrin α7β1 and dystroglycan contribute to force production in the muscle fibre. However, only the latter is involved in anchoring the basement membrane to the sarcolemma [58].

Congenital muscular dystrophy with integrin α7 deficiency

Integrin α7 chain is encoded by the *ITGA7* gene. Mutations in this gene have only been described in three patients who presented a recessive form of congenital myopathy characterized by delayed motor milestones and mental retardation for two of the three patients. Laminin α2 chain expression was normal in patient muscle but no integrin α7 subunit was present [13]. The consequences of the mutation at the molecular level have not been studied, but analyses of a mouse model that lacks the α7 integrin chain have shown that this receptor is required to maintain myotendinous junctions [134]. The β1 integrin accessory molecule integrin-linked kinase also stabilizes the myotendinous junctions and protects skeletal muscle from stress-induced damage [138]. However, apart from integrin-linked kinase, not much is known concerning the identity and function of the linker proteins that connect integrin α7β1 to the actin cytoskeleton. In addition, the signalling cascades associated with integrin α7β1 in skeletal muscle remain largely undetermined, although one study demonstrated that integrin α7 deficiency is associated with a disruption of the Ras–MAPK signalling pathway [137]. Finally, α7β1 integrin expression is impaired in laminin α2 chain-deficient muscle, suggesting that integrin α7 insufficiency may also contribute to MDC1A pathogenesis [139,140].

Dystrophin

Structure and function

Dystrophin, composed of four distinct domains, is a 427 kDa cytoskeletal protein that is involved in attaching F-actin to the ECM [141] (Figure 6). The N-terminal extremity contains an actin-binding domain and is followed by a central rod domain, which also contains an actin-binding site [142], a cystein-rich domain and the C-terminal extremity. The rod domain encompasses 24 spectrin-like repeats that provide flexibility to the molecule. Recently, it was demonstrated that neuronal NOS (nNOS, a key enzyme involved in the production of NO) binds directly to two spectrin-like repeats in dystrophin [143]. A small subregion (WW domain) composed by 30 amino acids links the central rod domain to the cystein-rich domain and provides a binding site for proline residues and binding to β-dystroglycan occurs within this part of the molecule [144]. Furthermore, the cystein-rich domain harbours two EF-hand motifs for intracellular calcium fixation and a calmodulin binding site. Finally, the C-terminal extremity is composed by two coiled-coil domains involved in the oligomerization of the molecule and it also contains binding sites for dystrobrevins and syntrophins [145–148]. Multiple smaller isoforms of dystrophin sharing the same C-terminal extremity are transcribed from several intronic promoters within the dystrophin gene [149]. Furthermore, utrophin is a 395 kDa dystrophin homologue that is widely distributed and contains the same four domains as dystrophin [21,150,151].

Duchenne and Becker muscular dystrophies

DMD (MIM ID No. 310 200) and Becker muscular dystrophy (BMD, MIM ID No. 300 376) are allelic disorders caused by mutations in the dystrophin gene [152]. The phenotypic difference between DMD and BMD patients can mostly be explained by the type of mutations and the resulting consequences at the protein level. Generally, DMD patients exhibit an absence of dystrophin while BMD patients often harbour internally deleted but partially functional dystrophin proteins [153–155].

DMD is a severe form of muscular dystrophy with an onset around 3 years of age. It is characterized

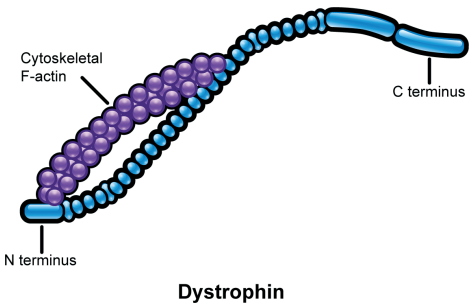

Figure 6. Representation of dystrophin. Dystrophin is composed of an N-terminal domain, a long central rod domain containing spectrin repeats, a cystein-rich domain and finally a C-terminal domain. F-actin binding sites are located in the N-terminal and in the rod domain. β-Dystroglycan binds to the cystein-rich domain, whereas binding sites for syntrophins and α-dystrobrevin are located in the C-terminal extremity.

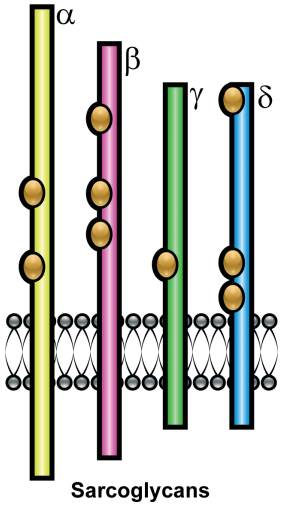

Figure 7. Simplified diagram of the sarcoglycans. β-, γ- and δ-sarcoglycan have a C-terminal extracellular domain, but for α-sarcoglycan it is the N-terminal domain. Brown ovals denote *N*-glycosylation moieties.

by progressive wasting of skeletal muscles, eventually resulting in cardiac and respiratory failure during the twenties age range [155]. Patients usually lose independent ambulation in the second decade of life. BMD is similar to DMD in the distribution of muscle wasting and weakness, which is mainly proximal, but the course is more heterogeneous than in DMD. The onset of the disease is generally later during childhood compared to DMD. Some patients have no symptoms until later in life but others can be more affected [155–157]. In this group, important genotype–phenotype correlations have been described regarding the onset of muscular, cardiac and cognitive impairment [154].

In DMD patients and in the *mdx* mouse model of dystrophin deficiency, loss of dystrophin results in a major reduction of the entire DGC complex, and thereby the link between the muscle fibre cytoskeleton and the ECM is destabilized and the sarcolemma becomes fragile. It is hypothesized that the brittle sarcolemma renders the muscle fibre less resistant to mechanical stress, which in turn leads to escalating fibre damage with membrane leakage and altered calcium homeostasis (through membrane tears, due to loss of sarcolemmal stability and/or disrupted calcium channels) and subsequent cell death [19,20]. Yet, dystrophin deficiency may cause pathology by other mechanisms as well. For example, in the absence of dystrophin, nNOS is lost from the sarcolemma. As nNOS produces NO that diffuses to the muscle vasculature and promotes blood vessel dilatation and improves blood flow into skeletal muscle, dystrophin deficiency has been associated with muscle ischaemia [158]. Furthermore, absence of nNOS at the sarcolemma also increases exercise-associated fatigue [143,159].

Sarcoglycans

Structure and function

Sarcoglycans are single-pass transmembrane glycoproteins that belong to the DGC and, through multiple interactions, serve as anchorage for the peripheral DGC components. They display a short intracellular tail, and a large extracellular glycosylated domain rich in cystein residues. This cystein cluster is conserved in all sarcoglycans and seems to be crucial for the assembly in a subcomplex (Figure 7) [160]. Six sarcoglycans (α, β, γ, δ, ε and ζ) have been described and α-, β-, γ- and δ-sarcoglycan form a tight subcomplex within skeletal muscle, while ε-, β-, γ- and δ-sarcoglycan form a tight subcomplex within smooth muscle [161,162]. ζ-Sarcoglycan is the most recently identified sarcoglycan family member and is expressed in both striated and smooth muscle [163]. The sarcoglycans are cotranslationally translocated in the endoplasmic reticulum and the assembly into the subcomplex occurs during the transport from the Golgi to the plasma membrane [160,161]. At the sarcolemma, the sarcoglycan complex interacts with other DGC members as well as with other proteins, including γ-filamin. In addition, the sarcoglycan complex has been shown to cooperate with integrins in mediating cell adhesion, at least *in vitro* [164]. Yet, the precise mechanical and/or signalling functions of the sarcoglycan complex remain to be elucidated.

Sarcoglycanopathies

Sarcoglycanopathies are a group of autosomal recessive muscular dystrophy caused by mutations in one of the four sarcoglycan genes [26–30]. Mutations in the genes encoding α-, β-, γ- and δ-sarcoglycan are associated with limb-girdle muscular dystrophy type 2D (LGMD2D, MIM ID No. 608 099), 2E (LGMD2E, MIM ID No. 604 286), 2C (LGMD2C, MIM ID No. 253 700) and 2F (LGMD2F, MIM ID No. 601 287), respectively. Limb-girdle muscular dystrophy is a group of progressive muscle disorders predominantly affecting proximal muscles around the scapular and

pelvic girdles. The clinical phenotype of sarcoglycanopathies is very heterogeneous regarding onset, progression and severity [165]. Generally, patients present progressive weakness and muscle degeneration, leading to loss of ambulation, respiratory failure and often premature death. Due to their simultaneous synthesis, defects in each sarcoglycan result in a complete destabilization of the entire sarcoglycan complex [160,161]. Furthermore, absence of the sarcoglycan complex at the sarcolemma leads to diminished α-dystroglycan expression [166]. Several putative mechanisms underlying the pathogenesis of sarcoglycan-deficient muscular dystrophy have been revealed by studies in animal models. They include loss of membrane integrity, calcium channel dysregulation, mitochondrial dysfunction and vascular abnormalities [166–171].

Development of treatment

There is currently no treatment for muscular dystrophy. Yet, improved disease management (eg non-invasive ventilation to improve respiratory function) has significantly prolonged life for patients with muscular dystrophy. Moreover, corticosteroids have been demonstrated to improve walking and increase quality of life for patients with DMD. However, the side-effects of corticosteroids are quite severe [172]. Thus, there is an urgent need to develop therapies for muscular dystrophy.

Several of the ECM and ECM-associated proteins discussed in this review were identified decades ago (eg collagen IV was identified in 1966; laminin in 1979; dystrophin in 1987; dystroglycan in 1992) [3,25,61,109]. The structure and function of laminins, collagens, dystroglycan, integrin, dystrophin and sarcoglycans have been extensively studied and mutation analyses have been performed by numerous research laboratories around the world. Moreover, generation and characterization of animal models of laminin α2 chain-deficient muscular dystrophy, Ullrich congenital muscular dystrophy/Bethlem myopathy, dystroglycanopathies, integrin α7-deficient muscular dystrophy, DMD/BMD and sarcoglycanopathies, respectively, have also significantly contributed to understanding the pathogenetic mechanisms of these disorders (Table 1 and references therein). Still, numerous questions as to the molecular and cellular consequences of the protein deficiencies and how they lead to muscular dystrophy persist. Nevertheless, the preceding biochemical and molecular work have laid the foundation for development of molecular therapeutic strategies targeting these incapacitating disorders. These approaches can be divided into the categories of gene replacement therapy, cell therapy and mutation-specific strategies. In Table 1, we present therapies that have had success in animal models and human explants and that have been tested in clinical trials. Considering that the linkage between the ECM and the cytoskeleton is disrupted in laminin α2 chain-deficient muscular dystrophy, Ullrich congenital muscular dystrophy/Bethlem myopathy, dystroglycanopathy, integrin α7-deficient muscular dystrophy, DMD/BMD and sarcoglycanopathy, many approaches have been aimed at restoring this connection. The idea has been to replace the mutated protein with a functional copy or smaller versions thereof or to replace the defective protein with a structurally and functionally similar protein. Indeed, there are several successful examples of gene replacement therapy, using transgenic mouse models as well as virus-mediated gene therapy described in Table 1. Also, the downstream effects of the perturbed interactions, such as increased apoptosis, have been addressed. Indeed, suppression of apoptosis has been beneficial in mouse models of several forms of muscular dystrophy (Table 1). Finally, a number of other possibilities aiming at correcting dystrophin mutations have been explored. Around 15% of DMD patients display mutations inducing a premature stop codon. In these cases, stop codon read-through has been forced by the use of gentamicin and PTC124 in *mdx* mice followed by clinical trials. Nevertheless, it appears that these drugs still need some improvement before clinical use, in particular since the results of the Phase IIb clinical trial with PTC124 were not encouraging (participants did not show significant increases in the 3 min walking distance test; Table 1 and references therein). However, manipulating the dystrophin gene splicing by antisense oligonucleotides, in order to exclude a mutated exon and restore the open reading frame and allowing the production of a partially deleted but functional dystrophin, has been successful and led to Phase III patient trials (Table 1).

Conclusion

An enormous amount of data on the structure and function of laminin α2 chain, collagens type IV and VI, dystroglycan, integrin α7β1, dystrophin and α-, β-, γ- and δ-sarcoglycans have accumulated since the discovery of these proteins. In addition, proteoglycans that are essential components of the ECM may be implicated in the development of muscular dystrophy, as the expression of several proteoglycans is enriched in fibrotic areas of dystrophic muscles [173–176]. Also, syndecan cell surface proteoglycans appear to be essential for skeletal muscle regeneration, a feature that is impaired as muscular dystrophy progresses [177]. Finally, a great deal is known regarding the pathogenetic mechanisms underlying laminin α2 chain-deficient muscular dystrophy, Ullrich congenital muscular dystrophy/Bethlem myopathy, dystroglycanopathies, integrin α7-deficient muscular dystrophy, DMD/BMD and sarcoglycanopathies, respectively. Yet, no cure is available for these diseases, although vast progress is being made using several different lines of attack. Therefore, continued studies

Table 1. Current emerging therapies evaluated in preclinical studies and/or human trials

Mutated protein	Emerging therapy	Method	Species	References
Laminin α2 chain	Gene over-expression	Mini-agrin	Mouse model	[178–180]
		Laminin α1 chain	Mouse model	[181–183]
		Laminin α2 chain	Mouse model	[184]
		Insulin-like growth factor 1	Mouse model	[185]
		Integrin α7	Mouse model	[186]
		Galgt2	Mouse model	[187]
	Apoptosis suppression	Over-expression *BCL2*	Mouse model	[188]
		Omigapil	Mouse model	[189]
		Doxycycline	Mouse model	[190]
		Cyclophilin D deletion	Mouse model	[170]
	Proteasome inhibition	MG-132	Mouse model	[59]
	Autophagy inhibition	3-Methyladenine	Mouse model	[60]
	Stop codon read-through	Laminin α2 chain	Patient myotubes	[191]
	Cell-based therapy	Bone marrow transplantation	Mouse model	[192]
		$CD90^+$ cell transplantation	Mouse model	[193]
Collagen VI	Apoptosis suppression	Cyclosporine A	Mouse/Patient trials	[93, 194–196]
		Debio 025	Mouse model	[197]
	Stop codon read-through	siRNA against SMG-1 or Upf1	Patient fibroblasts	[198]
	Autophagy stimulation	Gene expression, diet and drugs	Mouse model	[108]
α-Dystroglycan	Gene over-expression	*LARGE*	Mouse model	[116,199;
Integrin α7	Protein delivery	Laminin-111	Mouse model	[200]
Dystrophin	Gene over-expression	Dystrophin (full length/μ/mini)	Mouse model	[201–204]
		AAV dystrophin	Mouse/dog/primate/patients	[205–212]
		Lentivirus dystrophin	Mouse/dog/primate model	[213–220]
		Utrophin	Mouse model	[221–224]
		Sarcospan	Mouse model	[225]
		Integrin α7	Mouse model	[226]
		Galgt2	Mouse model	[227,228]
		ADAM12	Mouse model	[229,230]
		nNOS	Mouse model	[231,232]
		Calpastatin	Mouse model	[233]
		SERCA1	Mouse model	[234]
	Stop codon read-through	Gentamicin	Mouse/Patient trials	[235–240]
		Ataluren (PTC124)	Mouse/Patient trials	[241,242]
	Exon-skipping	2′-*O*-Methylphosphorothioates	Mouse/Patient trials	[243–248]
		Morpholinos	Mouse/Patient trials	[249–260]
		AAV (U7snRNA or U1)	Mouse/dog model	[261,262]
	Naked DNA delivery	Muscle/vein injection	Mouse/dog/primate model	[263–270]
		Electroporation	Mouse/dog model	[271–273]
	Restoration reading frame	Meganucleases	Mouse model	[274]
	Utrophin up-regulation	Drug induction	Mouse model	[275–277]
	Cell therapy	Myogenic/satellite cells	Mouse/dog/patient trials	[278–287]
		Muscle-derived stem cells	Mouse model	[288,289]
		Bone marrow stem cells	Mouse model	[220,261,290–297]
		Side population	Mouse model	[298,299]
		Pericytes	Mouse model	[300,301]
		Mesoangioblasts	Mouse/dog model	[216,302–303]
		Placenta-derived cells	Mouse model	[304]
		iPS cells	Mouse model	[305]
	Myostatin inhibition	Antibodies	Mouse/patient trials	[306,307]
		Inhibitors	Mouse model	[308,309]
		Inactivation myostatin receptor	Mouse model	[310–312]
		Myostatin pro-peptide	Mouse model	[313–315]
	Protein delivery	Laminin-111	Mouse model	[316–318]
		Biglycan	Mouse model	[176]
	Akt pathway stimulation	Valproic acid	Mouse model	[319]
	Proteasome inhibition	Drug targeting	Mouse model/patient explants	[320–323]
	Apoptosis suppression	Debio 025	Mouse model	[170]
	Inflammation and NO	HCT 1026	Mouse model	[324]
	ROS scavenging	Tiron/PP2	Mouse model muscle fibers	[325]
	IGF-1	Systemic delivery	Mouse model	[326]
	L-Arginine	Systemic delivery	Mouse model	[327]
	Angiotensin II regulation	Losartan	Mouse model	[328,329]
	MMP inhibitors	Batimastat	Mouse model	[330]
	TNFα reduction	Eicosapentanoic acid	Mouse model	[331]
	NF-κB inhibition	Pyrrolidine dithiocarbamate	Mouse model	[332]

Table 1. (*Continued*)

Mutated protein	Emerging therapy	Method	Species	References]
α-Sarcoglycan	Gene over-expression	α-sarcoglycan rAAV/AV vector	Mouse/patient trials	[333–339]
		Galgt2	Mouse model	[340]
		ε-sarcoglycan	Mouse model	[341]
	Inflammation and NO	Ibuprofen and NO co-treatment	Mouse model	[324,342,343]
	Cell therapy	Mesoangioblasts	Mouse model	[344]
	Proteasome inhibition	Velcade	Patient muscle explants	[345]
	Muscle wasting prevention	Myostatin inhibition	Mouse model	[309,346]
β-Sarcoglycan	Gene over-expression	β-sarcoglycan rAAV/AV vector	Mouse model	[339,347]
γ-Sarcoglycan	Gene over-expression	γ-sarcoglycan rAAV vector	Mouse model	[348]
δ-Sarcoglycan	Gene over-expression	δ-sarcoglycan rAAV/AV vector	Hamster/mouse model	[347,349–352]
		SERCA1	Mouse model	[353]
	Cell therapy	Transplantation	Hamster/mouse model	[354]
	Mitochondrial function	MPTP protection	Mouse model	[173]
	Apoptosis suppression	Cyclophilin D/Debio 025	Mouse model	[170]
	Membrane integrity	Omega-3 fatty acid diet	Hamster model	[355]

of the ECM–cell membrane–cytoskeleton interactions in skeletal muscle remain fundamental to in order to develop treatment for the muscular dystrophies.

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Author contributions

VC and MD wrote the manuscript jointly.

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