Background

Skeletal muscle is the largest organ in the human body, comprising up to 40% of the total body mass. It is present in animals from microscopic insects up to blue whales traversing the oceans. Regardless of species, skeletal muscle’s main function is to drive locomotion. More than four decades ago Huxley and Simmons pioneered the sliding filament model of force generation in striated skeletal muscles by demonstrating that thick (myosin) and thin (actin) filaments interact to form actomyosin cross-bridges, which generate muscle contraction.\(^1\) Myosin and actin filaments are organized into sarcomeres, the functional units of muscle contraction.\(^2\) Series of sarcomeres form myofibrils, which assemble in proximity to each other into muscle fibers during myogenesis.\(^3\) Myofibrils constitute the major compartment (~80%) of the muscle volume.\(^4\) Each muscle fiber is bounded by a plasma membrane (sarcolemma) shielding the intra- and extracellular compartments. Neighboring muscle fibers are organized into fascicles or muscle fiber bundles, encased by the perimysium and spanning the length of the muscle, from tendon to tendon. Finally, the whole muscle is ensheathed by the epimysium (Fig. 1).\(^5\) Together, the perimysium and the epimysium form myotendinous junctions, a distinct structure that extends from the muscle fibers into the tendon. At ultrastructural level the myotendinous junctions display finger-like interdigitations and invaginations, like folded hands, with the purpose of increasing the contact surface between the two types of tissues. Longitudinal force (tendon-tendon) is transmitted at the myotendinous junctions.\(^6\)

To secure proper muscle function and to protect against contraction-induced damage, the actin cytoskeleton of the muscle fiber is linked to an extracellular protein matrix layer: the basement membrane (Fig. 1). The basement membrane is a thin and highly specialized sheet of extracellular matrix surrounding muscle, fat, peripheral nerve cells and covering the basal side of epithelial and endothelial cells.\(^7\) At the ultrastructural level the basement membrane consists of two layers: the basal lamina and the reticular lamina. The reticular lamina is composed mainly of collagen and is intimately connected to the neighboring endomysium. The basal lamina on the other hand is directly linked to the sarcolemma and typically possesses an electron-lucent layer (lamina lucida) and an electron-dense layer (lamina densa).\(^8\) Laminin, a large (400–900 kDa) heterotrimeric extracellular glycoprotein, is a major constituent of the basal lamina together with type IV collagen. Laminin-211 (formerly named merosin) is the most abundant laminin isoform in the basement membrane of adult skeletal muscle.\(^9,10\) However, additional laminin isoforms are present during myogenesis and at junctional regions of the muscle fiber such as the neuromuscular junction and the myotendinous junction.\(^11\) In this review, we focus on the roles of laminin-211 in skeletal muscle function.

Laminin-211 and Friends

Early studies on Engelbreth-Holm-Swarm (EHS) mouse sarcoma and mouse parietal yolk sac carcinoma resulted in the isolation and identification of laminin more than 30 years ago.\(^12,13\) Laminins consist of three similar but non-identical polypeptide chains (α, β and γ), which assemble into a four-armed crucifix- or T-shaped heterotrimer with two or three short arms and one long arm (Fig. 2).\(^14\) To date, five different laminin α-chains, three β-chains and three γ-chains have been demonstrated to assemble into at least 16 different isoforms in vivo.\(^15\) In 1990, Eva Engvall and colleagues identified the third laminin isoform, now known as

**Keywords:** basement membrane, dystroglycan, integrin, laminin, muscle force, sarcolemma, skeletal muscle

**Abbreviations:** DG, dystroglycan; EDL, extensor digitorum longus; LG, laminin-type G domains; MDC1A, congenital muscular dystrophy type 1A; PI3-K, phosphatidylinositide 3’-OH kinase; SG, sarcoglycan; SSPN, sarcospan; WT, wild type

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A chain is no stronger than its weakest link is an old idiom that holds true for muscle biology. As the name implies, skeletal muscle’s main function is to move the bones. However, for a muscle to transmit force and withstand the stress that contractions give rise to, it relies on a chain of proteins attaching the cytoskeleton of the muscle fiber to the surrounding extracellular matrix. The importance of this attachment is illustrated by a large number of muscular dystrophies caused by interruption of the cytoskeletal-extracellular matrix interaction. One of the major components of the extracellular matrix is laminin, a heterotrimeric glycoprotein and a major constituent of the basement membrane. It has become increasingly apparent that laminins are involved in a multitude of biological functions, including cell adhesion, differentiation, proliferation, migration and survival. This review will focus on the importance of laminin-211 for normal skeletal muscle function.
Figure 1. Schematic diagram of extracellular matrix organization in skeletal muscle. Each muscle is covered by epimysium, a connective tissue layer that is continuous with the tendons that attach the muscles to the bones. The perimysium separates muscle fiber bundles (fascicles) and is mechanically connected to the epimysium at the surface. The muscle fibers are surrounded by a sarcolemma (plasma membrane) and a basement membrane. At the ultrastructural level the basement membrane consists of two bands: reticular lamina and basal lamina. The basal lamina can be further divided into lamina lucida and lamina densa. The basement membrane is approximately 30–50 μm thick. Individual muscle fibers are separated by endomysium.
Laminin is a mosaic protein with several domains critical for correct basement membrane assembly and function. A crucial step in the development of basement membrane is laminin polymerization, a process dependent on the globular LN domains at the N-terminal end of the three short arms and facilitated via interactions between the COOH-terminal long arm and receptors on the cell surface (Fig. 2). The majority of integrins involved – integrins – bind to laminin-211. Reports have shown that binding of integrins is non-covalently linked to laminin, a transmembrane protein that binds to dystrophin inside the cell, which in turn binds to the actin cytoskeleton.

The biological functions of the laminins are to a large extent dependent on binding to receptors on the cell surface. There are two major groups of laminin-211 receptors: integrins and non-integrins. Integrins are αβ heterodimeric transmembrane proteins involved in a multitude of functions such as adhesion, migration and differentiation. The major of integrins involved in cell-extracellular matrix adhesion shares a common β1 subunit. The main integrin in adult skeletal muscle is α7β1. Integrins contain a long extracellular domain and a relatively short cytoplasmic domain. Both subunits bind to ligands outside the cell. In addition, several subunits have alternatively spliced cytoplasmic domains. One example is the α7 subunit, which is present as α7A and B in mouse and human adult skeletal muscle.

Figure 2. Schematic of laminin-211 and binding sites for extracellular molecules. Laminin-211 is composed of one α2 chain (red), one β1 chain (blue) and one γ1 chain (green). Each short arm contains an N-terminal domain (LN) necessary for self-polymerization. Laminin α2 chain binds to heparin, sulfatides, perlecan and fibulin-1 via a tandem repeat of five G domain (LG) modules (LG1–5) at the C-terminus. The laminin γ1 chain also contains binding site for nidogen. Agrin binds to the coiled-coil domain of laminin.

Laminin-211 is Required for Muscle Integrity

Mutations in the gene encoding laminin α2 chain (LAMA2) cause congenital muscular dystrophy type 1A (MDC1A) (MIM ID #607 855). Congenital muscular dystrophy is a heterogeneous group of disorders characterized by hypotonia and muscle weakness, usually present at birth or in early childhood. The incidence has been estimated between 0.7:100,000 and 2.5:100,000 based on samples from Italy and western Sweden, respectively. MDC1A is the most common childhood congenital muscular dystrophy in the European population accounting for 30–50% of all congenital muscular dystrophies.
Integrin $\alpha 7\beta 1$ is a major laminin-211 receptor in skeletal muscle. Laminin-211 binding to integrin $\alpha 7\beta 1$ promotes activation of PI3-K/Akt and Ras/Raf/MEK/Erk cell survival pathways (among others). Akt is well known for its critical regulatory role in numerous cellular processes, including inhibition of pro-apoptotic and pro-autophagic signals such as FoxO, Bad and Bax. Integrin $\alpha 7\beta 1$ can also activate the Ras pathway resulting in upregulation of Bcl-2 expression. Arrows indicate activating events, whereas perpendicular lines indicate inhibitory events. FAK, focal adhesion kinase; Grb2, Growth factor receptor-bound protein 2; PI3-K, phosphatidylinositol 3-kinase; MEK, mitogen-activated protein kinase (MAP) kinase; Erk, extracellular regulated kinase; MuRF-1, muscle-specific RING finger 1; Atg, autophagy related genes; Bad, Bcl-2-associated death promoter. Note that some components of the basement membrane and integrin and Akt signaling pathways are excluded in the schematic for reasons of clarity.

Figure 3. Integrin $\alpha 7\beta 1$ is a major laminin-211 receptor in skeletal muscle. Laminin-211 binding to integrin $\alpha 7\beta 1$ promotes activation of PI3-K/Akt and Ras/Raf/MEK/Erk cell survival pathways (among others). Akt is well known for its critical regulatory role in numerous cellular processes, including inhibition of pro-apoptotic and pro-autophagic signals such as FoxO, Bad and Bax. Integrin $\alpha 7\beta 1$ can also activate the Ras pathway resulting in upregulation of Bcl-2 expression. Arrows indicate activating events, whereas perpendicular lines indicate inhibitory events. FAK, focal adhesion kinase; Grb2, Growth factor receptor-bound protein 2; PI3-K, phosphatidylinositol 3-kinase; MEK, mitogen-activated protein kinase (MAP) kinase; Erk, extracellular regulated kinase; MuRF-1, muscle-specific RING finger 1; Atg, autophagy related genes; Bad, Bcl-2-associated death promoter. Note that some components of the basement membrane and integrin and Akt signaling pathways are excluded in the schematic for reasons of clarity.
Patients show muscle weakness, delayed motor development, joint contractures and defects in the peripheral and central nervous system. Most mutations in the \textit{LAMA2} gene cause complete deficiency in laminin \(\alpha_2\) chain but patients with partial deficiency have been reported. Complete absence of laminin \(\alpha_2\) chain generally results in more severe phenotypes compared with partial deficiency.

Mutations in the laminin \(\alpha_2\) chain lead to muscular dystrophy in other species than humans, including cats and dogs. However, causative mechanisms of MDC1A have mainly been studied in mice. There are currently five different mouse models for MDC1A: two spontaneous mutations in \textit{Lama2}, \textit{dy/dy}, \textit{dy}^{2J}/\textit{dy}^{2J}, two targeted mutations, \textit{dy}^{5K}/\textit{dy}^{5K}, \textit{dy}^{W}/\textit{dy}^{W}, and one N-ethyl-N-nitrosourea (ENU) induced mutation, \textit{dy}^{Emqf17}/\textit{dy}^{Emqf17}. The \textit{dy}^{2J}/\textit{dy}^{2J} mouse displays a mild muscular phenotype as a result of slightly reduced levels of a truncated laminin \(\alpha_2\) chain while the \textit{dy/dy} mouse presents with moderate muscular dystrophy due to reduced expression of laminin \(\alpha_2\) chain. The \textit{dy}^{5K}/\textit{dy}^{5K} and the \textit{dy}^{W}/\textit{dy}^{W} mice die around three and ten weeks of age, respectively, and display severe muscular dystrophy. The \textit{dy}^{5K}/\textit{dy}^{5K} mouse is completely deficient for laminin \(\alpha_2\) chain whereas the \textit{dy}^{W}/\textit{dy}^{W} mouse expresses severely reduced levels. Although low levels of laminin \(\alpha_2\) chain seem to be beneficial for muscle function, near-physiological amounts of laminin \(\alpha_2\) chain are required in skeletal muscle to prevent or correct muscular dystrophy. Similar to MDC1A patients, mice lacking laminin \(\alpha_2\) chain display a complex phenotype with decreased body mass and peripheral neuropathy in addition to myopathy. For more detailed summary of mouse models for laminin \(\alpha_2\) chain-deficiency, see reference 61.

An intact link between the intracellular cytoskeleton and the surrounding basement membrane is necessary to provide mechanical reinforcement to the sarcolemma during cycles of contraction and relaxation. Mutations in most of the components of the dystrophin-glycoprotein complex as well as in integrin \(\alpha_7\) subunit cause a variety of muscular dystrophies. For
example, mutations in the dystrophin encoding gene cause Duchenne muscular dystrophy and loss of any of the sarcoglycans results in limb girdle muscular dystrophies.\textsuperscript{62,63} Mutations in these components are usually associated with sarcolemmal disruption, which results in uncontrolled entry of extracellular fluid components into the fibers, especially calcium.\textsuperscript{9} Studies on dystrophin-deficient \textit{mdx} mice, the mouse model for Duchenne muscular dystrophy, demonstrate that rupture of the sarcolemmal results in entry of extracellular calcium with subsequent hypercontraction and contracture clots.\textsuperscript{64,65} However, the degree of sarcolemmal damage does not always seem to correlate with the severity of the muscle disease (Fig. 5). Several studies have demonstrated less sarcolemmal damage in \textit{dy/dy}, \textit{dy}\textsuperscript{2J}/\textit{dy}\textsuperscript{2J} and \textit{dy}\textsuperscript{3K}/\textit{dy}\textsuperscript{3K} muscles compared with \textit{mdx} mice, despite the extremely severe muscle phenotype associated with laminin \(\alpha_2\) chain-deficiency.\textsuperscript{66,67} This is unexpected as mutations in laminin \(\alpha_2\) chain lead to a fragmented or absent basement membrane.\textsuperscript{57,58} A recent report on a zebrafish model of MDC1A suggests that the severe muscle phenotype associated with laminin \(\alpha_2\) chain-deficiency arises from muscle fiber detachment rather than sarcolemmal rupture.\textsuperscript{68}

Notably, mice deprived of laminin-211 and patients with MDC1A maintain an intact dystrophin-glycoprotein complex (Fig. 5).\textsuperscript{58,69} Experiments based on mechanical peeling of single myofibers provided further support for this observation. In normal muscles and in muscles from laminin \(\alpha_2\) chain-deficient mice, costameric \(\gamma\)-actin is stably associated with dystrophin after membrane peeling.\textsuperscript{70,71} However, in muscles from \textit{mdx} mice, which display a drastic reduction of all the components of the dystrophin-glycoprotein complex (but not laminin-211), no costameric actin was retained after membrane peeling.\textsuperscript{70} Interestingly, the Large\textsuperscript{myd} mouse, which lacks the Large glycan structure on \(\alpha\)-dystroglycan necessary for binding to laminin \(\alpha_2\) chain, also maintains an intact dystrophin-glycoprotein complex and similar to laminin \(\alpha_2\) chain-deficient mice, displays detachment of the basement membrane and severe muscular dystrophy (Fig. 5).\textsuperscript{72-74} However, according to a study by Han and colleagues, muscle from Large\textsuperscript{myd} displayed comprised sarcolemmal integrity.\textsuperscript{74,75} Importantly, a recent report suggests that fiber composition has an impact on protection against contraction-induced injury.\textsuperscript{76} Extensor digitorum longus (EDL) and soleus muscle from Large\textsuperscript{myd} mice were subjected to a series of

\begin{figure}
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\caption{Schematic model of integrin \(\alpha_7\beta_1\) and the dystrophin-glycoprotein complex in health and disease. Laminin-211 binds two major receptors in skeletal muscle, integrin \(\alpha_7\beta_1\) and dystroglycan (DG), a core component of the dystrophin-glycoprotein complex. In healthy (WT) muscle, this binding provides a link between the cytoskeleton and the surrounding basement membrane. In laminin \(\alpha_2\) chain-deficient mice (\textit{dy}/\textit{dy}\textit{K}), the dystrophin-glycoprotein complex remains intact at the sarcolemma whereas integrin \(\alpha_7\beta_1\) is severely reduced. This leads to a slight destabilization of the sarcolemma. In contrast, \textit{mdx} muscle, the loss of dystrophin results in a secondary loss of all other components of the dystrophin-glycoprotein components. Importantly, despite a compensatory increase in integrin \(\alpha_7\beta_1\), dystrophin-deficiency leads to severe sarcolemmal damage. Large\textsuperscript{myd} mice lack the binding motif for laminin-211 but maintain integrin \(\alpha_7\beta_1\) and the dystrophin-glycoprotein complex at the sarcolemma. Still, the Large\textsuperscript{myd} mice are susceptible to contraction-induced damage to the sarcolemma. It should be noted that a recent study observed significant differences in sarcolemma damage between different muscles from Large\textsuperscript{myd} mice. The same study reported compensatory increase in integrin \(\alpha_7\beta_1\) expression in distinct muscles. SSPN, sarcospan; SGs, sarcoglycans. Primary and secondary deficiencies are depicted in gray.}
\end{figure}
eccentric contractions. The EDL muscle, consisting mostly of fast-twitch fibers, displayed a significant increase in force deficit, while no such difference was observed in the soleus muscle, which contains approximately equal number fast and slow fibers. Taken together, laminin-211 is important for muscle integrity and loss of laminin α2 chain results in a very severe muscular dystrophy. However, the muscle damage cannot be explained strictly by sarcolemmal damage, but seems to depend on additional factors. A reoccurring finding among muscular dystrophies is upregulation of compensatory proteins. For example, mice lacking dystrophin display increased levels of utrophin and integrin α7β1 (Fig. 5). Loss of laminin α2 chain results in a compensatory increase in laminin α4 chain, giving rise to laminin-411. However, the laminin α4 chain, which does not contain the N-terminal domain, cannot polymerize and does not bind to α-dystroglycan and consequently does not alleviate the muscular phenotype (Fig. 2). Importantly, agrin binds to both α-dystroglycan and to laminin. Accordingly, several studies have shown that mini-agrin can act as a linker between laminin-411 and α-dystroglycan in mice deficient for laminin α2 chain and significantly reduce the dystrophic pathology.

We have previously demonstrated that transgenic expression of laminin-111 in laminin α2 chain-deficient mice reduces muscular dystrophy and recent reports have identified laminin-111 as a protein therapeutic. Systemic administration of laminin-111 protein reduced muscle pathology in both dyw/dyw and mdx mice together with a reduced number of apoptotic cells in dyw/dyw mice. These results suggest that protein substitution therapy could serve as a future treatment of muscular dystrophy. Although promising, further research is required to better understand the molecular basis of laminin-111 protein therapy as transgenic overexpression of laminin-111 in mdx mice had no ameliorating effect on the dystrophic pathology.

It should be noted that additional studies have demonstrated partial redundancy between laminin pairs. One example is a mouse model for Pierson syndrome, a congenital nephritic syndrome caused by mutations in the gene encoding laminin β2. A recent report demonstrated that transgenic overexpression of laminin β1 rescued the laminin β2-deficient mice.

**Laminin Signaling**

Signaling through integrin α7β1 is important to promote cell growth and myofiber survival. Mutations in the α7 subunit result in congenital muscular dystrophy whereas overexpression of integrin α7β1 ameliorates muscle pathology in dystrophin-deficient mdx mice, partly due to activation of the phosphatidylinositol 3-’OH kinase (PI3-K)/Akt kinase cascade, involved in regulation of cell metabolism and survival. Lack of laminin α2 chain results in greatly reduced levels of integrin α7β1 at the muscle cell surface and in vitro experiments have shown that laminin-211 is necessary for stability and survival of myotubes. More specifically, laminin-211 upregulates the expression of apoptotic suppressors such as Bcl-2 and Bcl-XL and downregulates the expression of effectors (pro-apoptotics) such as Bax and Bak. In agreement with these findings, muscles from MDC1A patients typically display apoptotic cells. Treatment of dyw/dyw mice by inhibiting apoptosis, either through activation of the antiapoptosis protein Bcl2 and inactivation of the proapoptosis protein Bax, or pharmacological inhibition has beneficial effects on the muscle pathology.

Recent studies have also implicated laminin-211 signaling in regulation of protein synthesis and degradation. Loss of muscle leads to muscle atrophy, a recurrent finding in muscles from MDC1A patients. Investigation of muscles from dyw/dyw mice revealed a significant decrease in phosphorylated (active) Akt. The PI3-K/Akt cell survival and growth-promoting pathway controls proteasome activity in skeletal muscle and decreased Akt activity leads to muscle atrophy due to aberrant regulation of genes known to be part of the ubiquitin-proteasome system. Indeed, lack of laminin-211 resulted in inactivation of Akt and increased expression of transcription factor Foxo together with key ubiquitin ligases MuRF-1 and MAFbx (Fig. 3). A subsequent study demonstrated that a second pathway involved in degradation of proteins, the autophagy-lysosome pathway, is overactivated in dyw/dyw mice. Importantly, pharmacologic inhibition of the proteasome and autophagy, respectively, significantly reduced the dystrophic symptoms.

Less is known regarding laminin α2 chain signaling through dystroglycan and the dystrophin-glycoprotein complex. In a previous study we demonstrated that transgenic overexpression of laminin-111 in dyw/dyw mice restored integrin α7β1 expression with a concomitant amelioration of the muscle pathology. Importantly, laminin α1 chain also binds to integrin α7β1 and α-dystroglycan but is not normally expressed in the neuromuscular system. Importantly, laminin α1 and α2 chains utilize distinct LG domains for binding to α-dystroglycan: laminin-111 binds via LG4 whereas laminin-211 binds via LG1–3 and LG4–5. However, both laminin-111 and laminin-211 use the same domains for binding to integrin α7β1 (LG1–3). Overexpression of a modified laminin α1 chain lacking LG4–5 domains in dyw/dyw mice (δE3LMα1) provided a tool to investigate the roles of dystroglycan and integrins in the neuromuscular system in vivo. Selected muscles from the δE3LMα1 mouse were rescued (diaphragm and heart) but the limb muscles remained dystrophic. Interestingly, assembly of the basement membrane surrounding heart and diaphragm was not completely restored suggesting that a fully intact basement membrane is not critical for amelioration of the dystrophic phenotype. Taken together, this study implicates that interaction between dystroglycan and laminin is important for the survival of muscle fibers in selected muscles. Furthermore, it may be that dystroglycan is not involved in the downstream autophagy and proteasome degradation machinery, as the expression of autophagy- and proteasome-related genes is not increased in dystrophic δE3LMα1 limb muscles (and unpublished observation).

**Laminin-211 is Necessary for Force Transmission**

The basement membrane is important for transfer of contractile force. Disrupting the binding of laminin-211 to α-dystroglycan and integrin α7β1 in skeletal muscle results in a significant...
When the muscle contracts, force is transmitted from the myosin filament to the Z line, which forms the border of the sarcomere. In addition to connecting individual sarcomeres longitudinally, the Z lines are also connected to the sarcolemma and the basement membrane via costameres, a subsarcolemmal network of proteins that align in register with the Z line. The dystrophin-glycoprotein complex and integrin α7β1 are present throughout the sarcolemma but enriched at the costameres, where they connect the Z line to the endomysium. The firm association between extra- and intracellular compartments at the sites of costameres is evident as shortening of the muscle during contraction makes the sarcolemma bulge out slightly in between the costameres. There are numerous studies suggesting that contractile force can be transmitted laterally, from the sarcomeres across the sarcolemma to the extracellular matrix of the muscle (myofascial) in addition to longitudinally, from sarcomeres in series to the tendon (myo-tendinous). Almost 30 years ago Street performed elegant experiments on frog muscles, demonstrating evidence for myofascial force transmission. Furthermore, a significant degree of non-primate mammalian muscles contains fibers that do not extend from tendon to tendon but instead terminate within the muscle belly (intrafascicularly). These fibers have been shown to express integrin α7 subunit and dystrophin at the intrafascicular terminations, likely involved in force transmission via cell-extracellular matrix interactions. A recent study developed a technique to measure and compare lateral force in healthy, dystrophic and old muscles and reported a major decrease in both longitudinal and lateral force in dystrophic and old muscle, likely due to decreased interaction between the muscle cell and the surrounding basement membrane.

The importance of laminin for lateral transmission of muscle force is emphasized in skeletal muscle tissue engineering. Despite recent advances, bioengineered skeletal muscle has proven to be a major challenge. One major obstacle is the limited contractile function associated with skeletal muscle engineered in vitro. To circumvent this, a recent report investigated the impact of various combinations of extracellular matrix to improve muscle function. One of the main findings was that increasing the Matrigel content resulted in a 3-fold increase in force compared with controls. Matrigel is a solubilized basement membrane preparation extracted from Engelbreth-Holm-Swarm mouse sarcoma, composed mainly of laminin-111 together with type IV collagen, heparan sulfate proteoglycans and nidogen. Based on this, the authors suggested that the basement membrane and laminin are crucial components for muscle function. These and other findings emphasize the importance of laminin-211 and the basement membrane in force transmission.

**Conclusion and Future Perspectives**

Laminin-211 plays a pivotal role in muscle function. However, despite considerable progress, we are still only beginning to understand the vast number of biological processes that involve laminin. Loss of laminin α2 chain results in MDC1A, a devastating muscular dystrophy for which there still is no cure. Clearly, additional research is needed to find new therapies to approach muscle disorders. Of special interest is the role of laminin-211 in cell-extracellular matrix communication. Elucidating the effects of signaling anomalies in muscle disease has a potential to open novel paths of treatment strategies, not only applicable to muscular dystrophy but also to muscle atrophy due to disease or aging. Furthermore, the regenerative capacity of skeletal muscle via activation of satellite cells offers an exciting approach in alleviating muscle wasting. Insufficient regenerative capacity leads to replacement of muscle with non-muscle tissue with a concomitant loss of muscle function. Several studies suggest decreased regeneration in laminin α2 chain-deficient muscle. It is generally thought that ongoing cycles of muscle degeneration and regeneration finally depletes the pool of satellite cells. However, it is possible that loss of laminin-211 could affect satellite cells per se. The location of satellite cells between the sarcolemma and the basement membrane also speaks in favor for a role of laminin-211 in muscle regeneration. However, further research is needed to more precisely characterize the importance of laminin-211 in this aspect of muscle biology. Taken together, an improved understanding of the function of laminin-211 in muscle biology will be fundamental for developing future treatment strategies.

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