Costameres: the Achilles’ Heel of Herculean Muscle

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Like the ancient Greek hero Hercules, striated muscle is famous for performing impressive feats of strength. The procurement of food, breathing, and defense or escape from harm all depend on force production by skeletal muscle while contraction of cardiac muscle drives the circulatory system. As with the powerful Achilles, however, striated muscle possesses a small but mortal weakness. That weakness resides in the costamere, a relatively obscure element of the cortical cytoskeleton in striated muscle. The costamere has garnered new attention because several of its constituent proteins are defective in muscular dystrophies and cardiomyopathies. Furthermore, many costameric proteins physically interact with Z disk or sarcolemmal proteins, which also cause myopathies when missing or defective. Finally, several newly identified costameric proteins suggest a role for the costamere/Z disk axis in converting mechanical stimuli to alterations in cell signaling or gene expression. Here, I will summarize current understanding of costamere structure and function as well as its role in diseases of striated muscle.

**Costamere Structure and Function**

As originally described in the early 1980s (1;2), costameres are subsarcolemmal protein assemblies that circumferentially align in register with the Z disk of peripheral myofibrils and physically couple force-generating sarcomeres with the sarcolemma in striated muscle cells (Fig. 1). In addition to costameres, the cortical cytoskeleton of striated muscle contains much finer hoop-like domains aligned in register with the M line and longitudinal strands that appear to connect M line components with costameres (3). Although several constituents of costameres have also been detected in the M line and longitudinal elements (3), these cytoskeletal elements are not consistently observed so
information about their composition and putative function is minimal. Therefore, the use of the term costamere in this review refers only to peripheral Z disk structures as originally defined (1;2). A variety of data indicate that costameres are a striated muscle-specific elaboration of the focal adhesions expressed by nonmuscle cells. The canonical focal adhesion protein vinculin is also a founding member of costameres (1) and its immunofluorescence staining pattern in striated muscle remains the standard by which many other costameric proteins have been identified. Other focal adhesion proteins found in costameres include talin, α-actinin and β1 integrins (4). While not restricted to costameres, immuno-EM studies indicated that the intermediate filament protein desmin constitutes one of the physical links between the Z disk and sarcolemma (4).

Classic experiments by Street (5), Craig and colleagues (1) and the Sangers (6) suggest that costameres may function to laterally transmit contractile forces from sarcomeres across the sarcolemma to the extracellular matrix and ultimately to neighboring muscle cells. Lateral transmission of contractile force would be useful for maintaining uniform sarcomere length between adjacent actively contracting and resting muscle cells comprising different motor units within a skeletal muscle. It is also logical that the sites of lateral force transmission across the sarcolemma would be mechanically fortified to minimize stress imposed on the relatively labile lipid bilayer. Other results have long suggested that costameres may coordinate an organized folding, or “festooning” of the sarcolemma (3;5), which again may minimize stress experienced by the sarcolemmal bilayer during forceful muscle contraction or stretch.
Costameres in Diseases of Muscle

The importance of the costamere to normal muscle function has emerged from investigations into the causes of muscular dystrophies (7;8) and dilated cardiomyopathies (9). Dystrophin, the product of the gene that is defective in Duchenne muscular dystrophy, was the first disease-relevant protein shown to be enriched at costameres (3). Through its cysteine-rich and C-terminal domains, skeletal muscle dystrophin interacts with a biochemically stable, heteroligomeric protein complex that includes the integral membrane dystroglycan and sarcoglycan/sarcospan subcomplexes and subsarcolemmal dystrobrevins and syntrophins (7;8). The N-terminal and large middle rod domains of dystrophin act in concert to effect an extensive lateral association with actin filaments (10). While dystrophin is not required for the assembly of costameres, its absence in humans and mice leads to a disorganized costameric lattice and disruption of sarcolemmal integrity (7;8). Most notably, extensive data report dramatically increased movement of membrane impermeant molecules both into and out of dystrophin-deficient muscle cells (11;12) while functional studies have demonstrated that specific force production by muscle lacking dystrophin is decreased (13) and hypersensitive to lengthening, or eccentric contraction (14;15). Moreover, the force decrement exhibited by dystrophin-deficient muscle undergoing eccentric contraction positively correlates with acutely increased sarcolemmal permeability (14;15). Immunofluorescence analysis of mechanically peeled sarcolemma showed that dystrophin is tightly attached to the sarcolemma (16) and its presence is necessary for strong coupling between the sarcolemma and γ-actin filaments of costameres (17). With one notable exception (18, see below), ablation of other components in the
dystrophin complex that cause muscular dystrophy also cause defects in sarcolemmal integrity (19;20) (21). Thus, there is good evidence that the dystrophin complex functions to anchor the sarcolemma to costameres and stabilize the sarcolemma against physical forces transduced through costameres during muscle contraction or stretch.

The Growing Costameric Protein Network

An extensive list of costameric proteins and their putative molecular partners has been painstakingly documented by many laboratories over the past 20 years. Because elucidation of its molecular composition was drawn out over many years and performed by diverse groups, it may not be obvious just how complex the costameric protein assembly really is. In the spirit of proteomics, I have therefore attempted to illustrate the interacting protein network of costameres (Fig. 2), based mainly on results from immunofluorescence colocalization, co-immunoprecipitation and in vitro binding assays. In addition, the identification of novel costameric proteins has also recently surged from the results of two-hybrid screens. Based on the extensive array of interconnected actin binding and intermediate filament proteins apparent in Fig. 2, it would seem difficult to argue against a role for costameres in physically coupling the force-generating sarcomeres to the sarcolemma and beyond. More striking are the large number of structural proteins within costameres or adjoining structures that cause muscle disease when mutated or ablated. While the complexity of the network illustrated in Fig. 2 further suggests that costameric subcomplexes may perform specialized sub-functions, the subcomplexes likely don’t function independently but rather must integrate their functions with the network at large. Finally, given each protein’s interaction with a
unique set of costameric proteins, it seems likely that the cellular phenotypes caused by independent ablation of two interacting proteins may differ because the loss of each perturbs a different suite of interacting proteins.

As an immediate test of these ideas, it is worth re-examining the single instance where ablation of a dystrophin complex constituent (α-dystrobrevin) results in muscular dystrophy with minimal apparent sarcolemmal damage (18). When compared to dystrophin-deficient mdx mice, the results with α-dystrobrevin null mice certainly support the idea that the loss of two different interacting costameric proteins can result in unique phenotypic outcomes possibly due to disruption of distinct subsets of interacting proteins. In the absence of sarcolemmal damage, it was suggested that α-dystrobrevin (and the dystrophin complex) may play a non-mechanical, and perhaps signaling role in striated muscle (18). However, no defect in muscle cell signaling has been identified that can account for the dystrophic phenotype observed in α-dystrobrevin -/- muscle. Furthermore, several two-hybrid screens seeking to reveal candidate signaling molecules regulated by α-dystrobrevin have instead identified several novel intermediate filament proteins as α-dystrobrevin interactors (22-24). Two of these proteins, synemin (24) and syncoilin (25), also interact with desmin. Striated muscle of mice lacking desmin exhibits numerous structural and functional abnormalities (26;27). Most notably, desmin -/- muscle is weak (27-29) but shows no force drop after eccentric contraction (28;29). While explicit tests of increased sarcolemmal permeability have not been reported for desmin null muscle, the absence of force drop with eccentric contraction (28;29) suggests these mice may experience little membrane disruption compared to mdx mice exhibiting large force drops correlating strongly with increased
sarcolemmal permeability (14;15). Lateral force transmission is, however, greatly diminished in desmin null muscle (30). Taken together, these results suggest that α-dystrobrevin may participate in lateral force transmission through the costamere by coupling the intermediate filament cytoskeleton with the dystrophin complex. If dystrophin, α-dystrobrevin and desmin are all physically connected within the costamere, how then can we reconcile significant membrane damage observed in mdx muscle with the minimal membrane defect accompanying myopathies in α-dystrobrevin -/- and desmin -/- mice? In this instance, it is informative to consider individual protein function from the broader perspective of an integrated costameric protein network (Fig. 2). Ablation of each protein clearly perturbs the function of the network as evidenced by muscle phenotype. However, the observed cellular phenotypes may differ because the absence of each protein disrupts the sub-functions performed by different clusters of interacting proteins within the costamere. In the case of α-dystrobrevin and desmin, loss of either protein may uncouple lateral force transmission through costameres to primarily disrupt sarcomere function (i.e., decreased force production) while sparing membrane integrity. Like desmin -/- muscle, dystrophin-deficient muscle also exhibits diminished force production, suggesting a contribution to normal sarcomere function. However, sarcolemmal damage additionally manifests as a cellular defect in dystrophin-deficient muscle because dystrophin also functions to mechanically stabilize the sarcolemma against potentially damaging lateral forces, regardless of how force is transmitted through the costameric network.

The concept of dystrophin as a multi-dimensional mechanical element of costameres has recently received apparent challenge from results obtained with
transgenic *mdx* mice overexpressing neuronal nitric oxide synthase (nNOS) or truncated dystrophin constructs. In the former case, Tidball and colleagues (31) observed restoration of nitric oxide (NO) levels to normal and a dramatic reduction in several parameters of muscular dystrophy, including sarcolemmal damage. Additional experiments indicated that restoration of NO inhibited muscle inflammation, which the authors concluded is the overriding cause of membrane damage in *mdx* muscle. However, this study only measured passive uptake of a membrane impermeant dye into resting muscles without assessing whether the greatly increased contraction-induced sarcolemmal permeability of *mdx* muscle (14;15) was also corrected. In addition, the lower serum creatine kinase levels of 4 week-old *mdx* mice overexpressing nNOS were not significantly different from *mdx* mice at 3 months of age suggesting a delay in onset of sarcolemmal damage. Finally, this group (32) and others (33) had previously reported that elevated NO could induce upregulation of the costameric proteins talin, vinculin and the dystrophin homologue utrophin. Given that overexpression of utrophin has been shown to reverse the mechanical phenotypes of dystrophin-deficient muscle (34), including strong coupling between costameric actin and the sarcolemma (35), it seems as likely that normalization of NO levels may have mechanically stabilized the sarcolemma of *mdx* muscle through increased expression of other structural proteins within costameres. From yet another perspective, Chamberlain and colleagues (36) recently assessed whether the retinal isoform of dystrophin, Dp260, could rescue *mdx* muscle. Dp260 lacks the N-terminal actin binding domain and spectrin repeats 1-10, but retains the basic middle rod actin binding site (37). Dp260/*mdx* muscle showed normal retention of costameric actin on mechanically peeled sarcolemma, normal
resistance to contraction-induced injury and reduced inflammation and fibrosis. However, Dp260/mdx muscle exhibited evidence of muscle cell necrosis/regeneration compared to wild type controls and diminished force production similar to that measured in mdx muscle. Thus, like desmin -/- muscle, Dp260/mdx muscle exhibited a mechanical defect (decreased force production) without evidence of sarcolemmal damage. These examples all underscore the idea that the absence of sarcolemmal damage does not preclude a mechanical defect residing elsewhere in the myofiber cytoskeleton as the cause of muscular dystrophy. The challenge remains to develop methods to identify and measure non-sarcolemmal mechanical defects associated with the loss of costameric proteins.

**Dynamic Aspects of Costameres**

Just because costameres are essential mechanical elements of striated muscle does not mean that they are static or unchanging. For example, it was recently shown that the costameric component of γ-filamin is upregulated in dystrophin-deficient muscle (38). Another study demonstrated recruitment of filamin to focal adhesions experiencing local mechanical stress applied via collagen-coated magnetic beads (39). Taken together, these results suggest that the dystrophin-deficient costamere may “sense” increased mechanical stress and attempt to compensate through filamin recruitment. Three additional studies demonstrate more directly that mechanical tension is critical in regulating costameric protein expression, stability and organization. In the first (32), it was shown that the costamere constituents talin and vinculin are upregulated in response to muscle contraction through a mechanism involving nNOS (also a constituent of costameres). In the second study (40), isolated cardiac myocytes
were mechanically unloaded by inhibition of contraction with a calcium channel antagonist. Within 24 hours, costameric staining for vinculin and β1 integrin was abrogated, but could be recovered by wash-out of the inhibitor or by application of static stretch. In the third study (41), the normally transverse banding pattern of several costameric proteins (dystrophin, syntrophin and dystroglycan) was shown to dramatically reorient longitudinally in skeletal muscle after 3 days of denervation. The costamere reorganization induced by denervation could be reversed by electrical stimulation or application of muscle agrin. Interestingly, extracellular laminin-2 remained in the normal costamere orientation in denervated muscle suggesting that coupling between cell surface receptors of costameres and the extracellular matrix is under neural control. Overall, the results of these studies indicate that costameres are highly dynamic structures responsive to (and dependent on) mechanical, electrical and chemical stimuli.

Another spate of recent publications supports an exciting role for the costamere/Z disk axis in mechanotransduction, the dynamic process through which mechanical stimuli are sensed by muscle cells and converted into biochemical responses (42). The protein Csl/Smpx localizes to costameres (Fig. 2) in adult skeletal muscle (43) and is dramatically upregulated in response to passive stretch in vivo (44). Although its costameric binding partners are unknown and Csl/Smpx knockout mice exhibit no obvious muscle phenotype, in vitro experiments suggest that Csl/Smpx can enhance IGF-1-mediated activation of nuclear factor of activated T cells (NFAT) and myocyte enhancer-binding factor (MEF2) transcription factor families (43). The NFAT and MEF2 families are famous for regulating gene expression associated with striated
muscle hypertrophy and fiber type in response to several stimuli, including mechanical stress (45). Of related interest, NFATc was recently localized to the Z disk in unstimulated skeletal muscle fibers but translocated to the nucleus upon specific patterns of electrical stimulation (46). Certainly, electrical stimuli act in part through local changes in calcium near the Z disk (47). However, the stimulated muscles were also undergoing active contraction (47) so it is possible that the electrical stimulation protocol induced a specific mechanical stress that was communicated to NFATc by Csl/Smpx, or through its physical association with calcineurin and calsarcins (Fig. 2) (48;49). Still other results (50) suggest that nuclear translocation of NFATc may be perturbed in dystrophin-deficient muscle due to increased phosphorylation by the stress activated protein kinase (SAPK) JNK1. The binding of SAPK3 to costameric α-syntrophin (51) further tempts speculation that the dystrophin glycoprotein complex may somehow participate in signaling through stress-activated pathways. Alternatively, filamin binds to the upstream activator kinase of JNK1 (MKK4), while JNK activation is absent in filamin-deficient cells (52). Thus, it is possible that recruitment of γ-filamin to costameres in dystrophin-deficient muscle (38) leads to abnormal JNK1 activation and perturbation of transcriptional regulation by NFATc.

Finally, it remains to be determined how stimuli in the form of mechanical force may be converted into altered biochemical responses. Clearly, mechanosensitive ion channels provide one established mechanism at the interface between the cytoskeleton and membrane (42) but this alone seems unlikely to fully explain mechanotransduction at the costamere and Z disk, particularly deep within a myofiber. Alternatively, it has been suggested that physical distortion may reveal (or obscure) new binding sites within
a network of interacting proteins that could transiently bring together (or dissociate) signaling molecules with their effectors (53). In support of this possibility (at least in non-muscle cells), Sawada and Sheetz (54) recently demonstrated differences in the array of cytoplasmic proteins bound to Triton-extracted cytoskeletal “ghosts” adhered to flexible substratum that were stretched compared to unstretched specimens. This type of approach is certainly amenable to striated muscle, where it may confirm the costamere/Z disk axis as a critical site of mechanotransduction and identify the important molecular players. Future studies are certain to reveal even more apollonian features integrated within the Achilles’ heel of muscle.

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FIGURE LEGENDS

Figure 1. Cellular location of costameres in striated muscle. Shown in (A) is a schematic diagram illustrating costameres as circumferential elements that physically couple peripheral myofibers to the sarcolemma in periodic register with the Z disk. The protein composition of costameres is shown in expanded form in figure 2. Shown in (B) is an inside-out sarcolemma that was mechanically peeled from a single myofiber and stained with antibodies to γ-actin to reveal the costameric cytoskeleton. Bar, 10 µm. Panel B is reproduced from The Journal of Cell Biology, 2000, 150, 1209-1214 by copyright permission of The Rockefeller University Press.

Figure 2. Delineation of the costameric protein network (the hard way). Proteins illustrated were previously shown to co-localize with an established costameric protein and/or interact with a costameric protein. Numerous proteins co-distribute with the Z-disk throughout the core of the myofibrillar apparatus, but also overlap and biochemically interact with costameric proteins at the myofiber periphery. Proteins connected by lines have been reported to interact based on co-immunoprecipitation, in vitro binding assays, or by two-hybrid analysis. Genes that cause muscular dystrophy and/or cardiomyopathy when mutated in humans, or knocked-out in mice encode proteins highlighted in red. Ablation of the proteins highlighted in green caused no discernible muscle phenotype. Proteins outlined in blue have been implicated in regulating cell signaling and/or gene expression. Proteins primarily associated with the extracellular matrix, sarcolemma, or Z-disk are grouped within shaded areas. The complete bibliography supporting this figure is available as supplementary information in the online version at http://www.jbc.org/.
FIGURE 1

A

Myofibrils
Z-Disk
Costameres
Sarcolemma
A Band

B

Costameres

[Image of a myofibril structure with labels for Myofibrils, Z-Disk, Costameres, Sarcolemma, and A Band.]
Supplementary Material
Notes and References Supporting Fig. 2
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Aciculin

Costamere localization (1)
Binding to dystrophin (2)

α-Actin

Mutations causing muscle phenotype in humans (3)

γ-Actin

Costamere localization (4;5)
Binding to, and functional association with dystrophin (5;6)

α-Actinin

Review for binding to actin filaments, β1 integrin and vinculin (7)
Binding to MLP (8-12)
Binding to synemin (13)
Binding to dystrophin (14)
Binding to ALP (15)
Binding to Raver1 (16)
Binding to myopalladin (12)

Actinin Associated LIM Domain Protein (ALP)

Binding to α-actinin (15)
Cardiomyopathy in knockout mice (17), but no skeletal muscle phenotype (18)

Ankyrins

Costamere localization (19)
Review for binding to spectrin (20)
Binding to Na/K-ATPase (21)
Binding to desmin (22)
Although products of 3 distinct ankyrin genes localize to the sarcolemma and/or costameres, only ankyrin-3 (ankyrin-G) co-immunoprecipitates with Na/K-ATPase (23)
Ankyrin-2 (ankyrin-B) knockout mice exhibit musculoskeletal defects and neonatal myopathy although it is not clear that these phenotypes are due to the absence of ankyrin-2 from costameres (24)
Aquaporin-4 (AQP4)

While not yet demonstrated to be costamere-specific, aquaporin-4 is localized to the sarcolemma and is absent from the sarcolemma of dystrophin-deficient \textit{mdx} mice, \(\alpha\)-syntrophin knockout mice, and mice overexpressing an \(\alpha\)-syntrophin construct lacking its PDZ domain (25;26). Aquaporin-4 knockout mice exhibit no evidence of muscular dystrophy and normal water permeability (27).

BPAG1b

Binding to actin filaments and desmin, skeletal muscle weakness and sarcolemmal damage in \textit{dt/dt} mice (28)
See (29) for clarification of isoform nomenclature and tissue-specific expression

Calcineurin

Localization to Z disk and binding to calsarcin (30;31)
Binding to NFATc (32)

Calsarcins

Binding to \(\alpha\)-actinin (30;33;34)
Binding to \(\gamma\)-filamin (31;33;34)
Binding to telethonin (31;33)
Localization to Z disk and binding to calcineurin (30;31)
Binding to cypher (31)

CapZ

Review for binding to barbed end of actin filaments, localization of \(\beta\)1 isoform to Z disk and \(\beta\)2 isoform to costameres (35)
Binding to \(\alpha\)-actinin (9)

Cardiac Ankyrin Repeat Protein (CARP)

Binding to myopalladin (12)

Caveolin-3 (Cav-3)

Distribution overlaps with costameres (36)
Binding to \(\beta\)-dystroglycan C-terminus (37)
Binding to nNOS (38)
Muscular dystrophy in human patients with mutations in caveolin-3, and mice either deficient or overexpressing caveolin-3 (39;40)
**Collagens**

While an extracellular collagen matrix was found localized in register with the Z disks of striated muscle before costameres were first defined (41), only type IV (42) and type XIII (43) collagens have been localized to costameres. Collagens presumably interact with the sarcolemma through direct binding to integrins although this has not been demonstrated experimentally. Type VI collagen mutations cause Bethlem myopathy (44) Type XV collagen deficiency causes skeletal and cardiomyopathy (45)

**Chisel (Csl/Smpx)**

Costamere localization (46)  
Binding partners unknown  
Upregulated in response to prolonged passive stretch of skeletal muscle (47)  
Augmented NFAT and MEF2 activity when overexpressed in cultured myotubes although Csl knockout mice showed no overt muscle phenotype (46)

**Cypher**

Binding to α-actinin (10;11)  
Binding to calsarcin (31)  
Severe congenital myopathy in cypher knockout mice (48)

**Desmin**

Distribution overlaps with costameres (49)  
Binding to ankyrin (22)  
Binding to spectrin (50)  
Binding to synemin (13)  
Binding to desmuslin (51)  
Binding to syncoilin (52)  
Binding to plectin (53)  
Binding to BPAG1b (28)  
Binding to nebulin C-terminus (12)  
Striated muscle phenotypes in desmin knockout mice (54;55)

**Dysbindin**

Binding to α-dystrobrevin (56)
**α-Dystrobrevin (α-Db)**

- Binding to dystrophin (57-59)
- Binding to syntrophin (60)
- Binding to sarcoglycan/sarcospan complex (61)
- Binding to desmuslin (51)
- Binding to dysbindin (56)
- Binding to syncoilin (62)
- Muscle phenotype in knockout mice (63)

**Dystroglycan (DG)**

- Costamere localization (5;64-66)
- Copurification with dystrophin, sarcoglycan/sarcospan complex (67;68)
- Binding to laminin-2 (69;70)
- Binding to dystrophin C-terminus (71)
- Binding to caveolin-3 (37)
- Muscular dystrophy in dystroglycan chimeric mice (72)

**Dystrophin (DYS)**

- Localization to costameres (73-75)
- Co-purification with dystroglycan and sarcoglycan/sarcospan complexes (68)
- Binding to syntrophins (57;60;76;77)
- Binding to α-dystrobrevin (57-59)
- Binding to aciculin (2)
- Binding to γ-actin at costameres (5;6)
- Binding to α-actinin (14)
- Review of muscular dystrophies caused by dystrophin mutations in humans, dogs, or mice (78;79)

**Fibronectin**

- Weak, periodic staining in register with vinculin, but not consistently observed (4;42)
- Presumably associated with the sarcolemma through direct binding to α5β1 integrin

**γ-Filamin**

- Binding to integrins and actin filaments (7)
- Binding to calsarcins (31;33;34)
- Costamere overlap, binding to sarcoglycan/sarcospan complex (80)
- Costamere overlap, binding to myotilin (81)
- Binding to SHIP2 (82)
**Integrins**

β1D integrin isoform localized to costameres (83)

α7B integrin isoform localized to costameres (84)

Review for binding to α-actinin, γ-filamin and talin (7)

β1 integrin binding to melusin (85)

Co-immunoprecipitation of α5β1 integrin with sarcoglycan/sarcospan complex in L6 myotubes (86)

Review for binding to laminin-2 (87)

Increased α7β1 integrin expression in dystrophin-deficient mdx muscle (88)

Muscular dystrophy in α7 integrin knockout mice (89)

Congenital myopathy in patients with α7 integrin mutations (90)

Muscular dystrophy in α5 integrin chimeric mice (91)

Transgenic overexpression of α7 integrin ameliorates dystrophy in the dystrophin-deficient mdx mouse (92)

**Laminin-2**

Costamere localization (42;93)

Binding to α-dystroglycan (69)

Review for binding to α7β1 integrin (87)

Review of muscular dystrophies caused by laminin-2 mutations in humans or by genetic knockout in mice (78)

**Melusin**

Costamere localization, binding to β1 integrin (85)

**Muscle-specific LIM Protein (MLP)**

Dilated cardiomyopathy in knockout mice (94)

Binding to α-actinin (8)

Costamere localization, binding to β-spectrin (95)

Positive regulator of myogenic differentiation that redistributes from nucleus to cytosol during myotube formation/differentiation (96)

**Myopalladin**

Binding to α-actinin, CARP, nebulin C-terminus (12)

**Myotilin**

Binding to α-actinin (97)

Binding to γ-filamin (81)

Myotilin is mutated in limb girdle muscular dystrophy 1A (98)
**Nebulin C-terminus (Neb-CT)**

Binding to desmin and myopalladin (12)

**Na/K-ATPase**

Costamere localization dependent on spectrin (23;65)
Binding to ankyrin (21)
Co-immunoprecipitation with ankyrin-3 (23)

**Neuronal Nitric Oxide Synthase (nNOS)**

Costamere localization (99)
Binding to α-syntrophin (100)
Binding to caveolin-3 (38)
nNOS knockout mice exhibit no evidence of muscular dystrophy (101), however, transgenic overexpression of nNOS ameliorates dystrophy in the dystrophin-deficient mdx mouse (102)

**Nuclear Factor of Activated T Cells (NFATc)**

Direct binding to inactive calcineurin in unstimulated cells (32)
NFATc localizes to the Z disk of unstimulated muscle fibers but translocates to the nucleus in response to electrical stimulation (103)

**Plectin**

Distribution overlaps with costameres (104)
Review of interacting proteins (53)

**Raver1**

Localized to costamere in adult skeletal muscle, but redistributes from nucleus to cytosol during myotube formation/differentiation. Binds α-actinin, vinculin. Binding to PTB/hnRNP1 suggests a role in RNA processing or targeting (16)

**Sarcoglycan/Sarcospan Complex (SGC/SPN)**

Co-purification with dystroglycan complex (68)
Specific co-immunoprecipitation with α-dystrobrevin (61)
Binding to γ-filamin (80)
Co-immunoprecipitation with α5β1 integrin in L6 myotubes (86)
Review of muscular dystrophies caused by sarcoglycan mutations in humans or by genetic knockout in mice (78)
**Spectrin**

Costamere localization (4;73;105)
Review for binding to actin filaments and ankyrin (20)
Review for binding to plectin (53)
Binding to desmin (50)
Binding to MLP (95)

**Stress-Activated Protein Kinase-3 (SAPK3)**

Binding to α-syntrophin (106)

**Syncoilin**

Binding to α-dystrobrevin (62)
Costamere localization and binding to desmin (52)

**Synemin**

Distribution overlaps with costameres, binding to vinculin (107)
Binding to α-actinin and desmin (13)
Binding to α-dystrobrevin and desmin (51)

**Syntrophin**

Costamere localization (65;66)
Binding to dystrophin (57;60;76;77)
Binding to α-dystrobrevin (60)
Binding to nNOS (100)
Binding to actin filaments (108)
Binding to stress-activated protein kinase-3 (106)
Aquaporin-4 is absent from the sarcolemma of α-syntrophin knockout mice and mice overexpressing an α-syntrophin construct deleted its PDZ domain (26).
α-Syntrophin knockout mice exhibit no evidence of muscular dystrophy (109;110)

**Talin**

Costamere localization (111;112)
Review for binding to actin filaments, β1 integrins, and vinculin (7)

**Telethonin**

Binding to titin N-terminus (113)
Binding to calsarcin (31;33)
Mutations cause limb-girdle muscular dystrophy type 2G (114)
Titin N-terminus (Titin-NT)

Binding to α-actinin (115)
Binding to telethonin (113)
Titin mutations in patients with dilated cardiomyopathy (116)
Titin mutated in the mdm (muscular dystrophy with myositis) mouse (117)

E-Tropomodulin (E-Tmod)

Costamere localization and binding to actin (118)

Type-II SH2-domain containing inositol 5-phosphatase (SHIP2)

Binding to γ-filamin, colocalization with γ-filamin at Z disks and costameres (82)
No obvious muscular dystrophy phenotype but increased glucose tolerance and insulin sensitivity in SHIP2 knockout mice (119)

Vinculin

Costamere localization (120)
Review for binding to actin filaments, α-actinin and talin (7)
Binding to synemin (107)
Binding to Raver1 (16)
Mutations in metavinculin cause dilated cardiomyopathy in humans (121)

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