ASSOCIATION OF SYNCOILIN AND DESMIN

LINKING INTERMEDIATE FILAMENT PROTEINS TO THE DYSTROPHIN-ASSOCIATED PROTEIN COMPLEX

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We recently identified a novel protein called syncoilin, a putative intermediate filament protein that interacts with α-dystrobrevin, a member of the dystrophin-associated protein complex. Syncoilin is found at the neuromuscular junction, sarcolemma, and Z-lines and is thought to be important for muscle fiber integrity. Based on the similar protein structure and cellular localization of syncoilin and desmin, we proposed that these proteins interact in vivo. The data presented confirm an interaction between syncoilin and desmin and demonstrate their co-localization in skeletal muscle. Intriguingly, whereas these proteins interact, COS-7 cell expression studies show that desmin and syncoilin do not assemble into heterofilaments. Furthermore, fractionation assay and immunofluorescence study of H2K myoblasts and myotubes suggest that, unlike typical intermediate filament proteins, syncoilin does not participate in filament formation with any protein. However, it is possible that syncoilin is involved in the anchoring of the desmin intermediate filament network at the sarcolemma and the neuromuscular junction. This interaction is likely to be important for maintaining muscle fiber integrity and may also link the dystrophin-associated protein complex to the cytoskeleton. The dysfunction or absence of syncoilin may result in the disruption of the intermediate filament network leading to muscle necrosis. Syncoilin is therefore an ideal candidate gene for muscular dystrophies and desmin-related myopathies.

The muscular dystrophies are a group of clinically heterogeneous diseases characterized by muscle wasting. Mutations in various muscle genes have been shown to be responsible for such disorders. Duchenne muscular dystrophy is caused by deletions and mutations in dystrophin, which encodes a protein of 427 kDa expressed in skeletal and cardiac muscle and in brain (1, 2). In skeletal muscle, dystrophin is located at the sarcolemma, where it interacts with a number of proteins, including the α-dystrobrevins, to form the dystrophin-associated protein complex (DAPC) (3, 4). Many members of this complex have already been implicated in muscle disorders, demonstrating the importance of the DAPC in muscle function. It is widely held that one function of the DAPC is to provide a molecular link between the actin cytoskeleton and the extracellular matrix, thereby sustaining sarcolemmal integrity during muscle contraction (3, 5, 6).

We recently identified a new member of the DAPC, syncoilin, through its interaction with α-dystrobrevin-1 and -2 in muscle (7). Syncoilin is a 64-kDa protein found in skeletal and cardiac muscle and was proposed to be a member of the intermediate filament (IF) protein superfamily based on sequence analysis (7). IF proteins are characterized by their ability to form 10-nm-diameter filaments and form the basis of the higher eukaryotic cytoskeleton together with thin filaments and microtubules (for review, see Ref. 8). All IF proteins share a common structural organization, consisting of an N-terminal head domain, a C-terminal domain, and a highly conserved central rod domain. On the basis of sequence homology within this central region, IFs are classified into six groups, and syncoilin is most similar to type III and IV IFs such as α-internexin (7). Although syncoilin has the central coiled-coil domains typical of IF proteins, it failed to form filamentous structures in transfected COS-7 cells, suggesting that other factors may be required to initiate heteropolymeric filament formation (7). Whereas the patterns of expression of IFs vary, these proteins are often considered to play a role in structural support and the mechanical preservation of cellular space (for review, see Refs. 8 and 9). Desmin, for example, is the main IF protein in mature striated muscle cells and was postulated to maintain the integrity of muscle fibers by linking adjacent myofilibrils together and linking peripheral myofilibrils to the sarcolemma (10, 11). Its localization at the sarcolemma (10), the Z-lines (11), and the neuromuscular junction (NMJ) (12), where syncoilin is expressed, makes it an ideal candidate binding partner of syncoilin. In view of the structural roles generally performed by IF proteins, the association of syncoilin with α-dystrobrevin is important because it may provide an alternate route by which the DAPC links to components of the cytoskeleton, in this case, the IF network.

The aim of this study was to investigate our hypothesis that syncoilin is associated with IF proteins at the sarcolemma and the NMJ. We therefore performed a yeast two-hybrid assay with syncoilin as bait. Desmin was identified as a putative binding partner of syncoilin. This interaction was confirmed in vitro and in vivo, through co-localization and co-immunoprecipitation assays. The ability of desmin and syncoilin to inter-
act provides evidence for an important association between IF proteins at the Z-lines in muscle and the extracellular matrix via the DAPC. Mutations in the desmin gene cause myopathy together with cardiomyopathy (13). Syncoilin, like desmin, is up-regulated in some muscular dystrophies, making it a candidate gene for muscular dystrophy as well as cardiomyopathy.

**EXPERIMENTAL PROCEDURES**

**Generation of Bait Constructs**—A fragment of the syncoilin sequence encoding amino acids 146–end (GenBank™ accession number AL221942) was PCR-amplified using primers For5 (5′-ATGCGGCCGACCATATGATCCCACACACGG-3′) and Rev1 (5′-ATTCGGCCGCCCCCATATATTGTTTACGACCCATGCC-5′). The amplified product was subcloned into the Nhel/Not site (underlined above) of the yeast bait vector pDBLeu (Invitrogen) to generate Syn5.1:pDB in frame with the DNA-binding domain of the Gal4 protein.

**Library Screening**—The construct Syn5.1:pDB and 10–20 µg of a mouse skeletal muscle cDNA library (Invitrogen) were co-transformed into the yeast strain MaV203 (Invitrogen) and plated onto SC-Leu-Trp-His media (Sigma), containing 83 mM 3-aminotriazole (3-AT) (Invitrogen). Sequential transformation of these constructs was also performed. Co-transformed and sequentially transformed colonies were incubated for 2 days at 30 °C, replica-cleaned, and further incubated for 3 days. Growth was confirmed by re-streaking resultant colonies onto fresh 3-AT plates. Three master plates were created by patching colonies onto SC-Leu-Trp with yeast control strains (Harlequin). After blocking the membranes overnight at 4 °C, replica-cleaned, and further incubated for 3 days. One-hundred colonies were screened in two independent experiments, resulting in 106 clones.

**Immunoblotting**—The prey plasmids were confirmed by replica plating onto selection medium (5 µl SC-Leu-Trp-Ura and SC-Leu-Trp-His) and electroporated into DH10B electrocompetent cells (Invitrogen). The 5′ ends of the plasmids were sequenced using vector primer pDBFor (5′-GAATAAGTGCGACATCATCATC-3′) and pDBRev (5′-ATGCTAGC-ATTCTTAAACAGTCCC-3′). The amplified product was subcloned into the Nhel/Not sites of pCl-neo vector (Promega) to generate desc:pClneo, which was then sequenced to check for errors. The generation of the syncoilin (sync:pCIneo) and α-dystrobrevin-1 (m24 + vr3:pCIneo) expression constructs has been described previously (7). Constructs were purified using the Qiagen Plasmid Mini or Maxikit for transfection. COS-7 cells were seeded onto coverslips in 6-well plates at a density of 1 × 10^6 cells/well. After 18 h of cell growth, desc:pClneo, sync:pCIneo, and/or m24 + vr3:pCIneo were transfected into cells using FuGene-6 (Roche Molecular Biochemicals) following the manufacturer’s instructions. Cells were incubated for 18–24 h at 37 °C, washed with phosphate-buffered saline (PBS), and processed for immunofluorescence experiments.

**RESULTS**

**Identification of Desmin as a Potential Binding Partner of Syncoilin by Yeast Two-hybrid Analysis**

To elucidate the role of syncoilin in muscle, a yeast two-hybrid assay was performed to identify putative binding partners. The bait construct Syn5.1:pDB, containing the syncoilin coiled-coil and C terminus regions, was utilized to screen a skeletal muscle cDNA library. The full-length syncoilin cDNA was unsuitable because it nonspecifically activated transcription of the yeast reporter genes. A total of ~5.5 × 10^6 clones were screened in two independent experiments, resulting in >400 positive colonies. Interactions between bait and prey plasmids were confirmed by replica plating onto selection media and assaying for β-galactosidase activity. Fifty-six colonies demonstrated the expected phenotype; they grew vigorously on SC-Leu-Trp-Ura and SC-Leu-Trp-His + 100 µl 3-AT media, 5-FOA inhibited their growth, and they demonstrated β-galactosidase activity. Sequence analysis identified 30 clones that contained an entire coding sequence of desc, and 3 clones that contained various regions of desmin (nucleotide 238–904–, and 1029–end). A re-transformation assay was performed, in which the plasmid containing full-length desmin cDNA was co-transformed with the Syn5.1:pDB construct. The growth pattern of resultant yeast colonies was compared with control strains representing positive and negative interactors.
The interaction between syncoilin and desmin was examined in yeast using four selective systems: SC-Leu-Trp-His + 100 mM 3-AT, SC-Leu-Trp-Ura media, and SC-Leu-Trp-His + 100 mM 3-AT or SC-Leu-Trp-Ura media, and exhibited β-galactosidase activity, and 5-FOA inhibited their growth. When noninteractors were used (shown in the Negative column), colonies failed to grow on SC-Leu-Trp-His + 100 mM 3-AT or SC-Leu-Trp-Ura media, did not exhibit β-galactosidase activity, and grew on media containing 5-FOA. Full-length desmin clone co-transformed with Syn5.1:pDB resulted in yeast colonies that grew on SC-Leu-Trp-His + 100 mM 3-AT and SC-Leu-Trp-Ura media and exhibited β-galactosidase activity, and 5-FOA inhibited their growth. All four phenotypes are consistent with the behavior of an yeast reporter genes.

**Co-immunoprecipitation of Syncoilin and Desmin**

To confirm the interaction of syncoilin and desmin, a co-immunoprecipitation experiment was performed on mouse skeletal muscle protein extracts. Prior to the assay, the solubilities of the two proteins were assessed. Desmin was found mainly in the insoluble fraction, although a small amount was found to be soluble. Syncoilin, in contrast, was found primarily in the soluble fraction (data not shown). When co-immunoprecipitation experiments were performed on the soluble extracts, syncoilin was detected in the immune complexes generated using two different desmin antibodies (Fig. 2A). In the reciprocal experiment, the use of SYNC-FP resulted in the precipitation of desmin (Fig. 2B). A negative control lacking primary antibody resulted in no detection of desmin or syncoilin, indicating that protein G did not nonspecifically interact with either protein.

**Co-localization of Syncoilin and Desmin in Skeletal Muscle**

To demonstrate that syncoilin and desmin co-localize in normal muscle, the expression patterns of these proteins were assessed by immunofluorescence microscopy. Fig. 3 shows normal C57 BL/10 mouse cryosections double-stained with anti-syncoilin antibody SYNC-FP (Fig. 3, A and D) and anti-desmin antibody Y-20 (Fig. 3, B and E). The overlay of the two antibodies is shown in Fig. 3, C and F. Syncoilin, as reported previously (7), is concentrated at the NMJ of normal mouse skeletal muscle (as confirmed by double staining experiments with α-bungarotoxin; data not shown) and weakly stains the sarcolemma (Fig. 3A). On longitudinal sections, syncoilin was found at the Z-lines and along the sarcolemma (Fig. 3D). Desmin also displayed a similar staining pattern at the NMJ, the Z-lines, and the sarcolemma (Fig. 3, B and E). The overlay of both SYNC-FP and Y-20 (Fig. 3, C and F) confirms the co-localization of these probes and hence supports an interaction between syncoilin and desmin at the NMJ, Z-lines, and sarcolemma.

**In Vitro Expression Studies of Syncoilin and Desmin in COS-7 Cells**

**Immunofluorescence Microscopy**—To further investigate the interaction of syncoilin and desmin, mammalian expression constructs containing the entire open reading frames of syncoilin and desmin were transfected into COS-7 cells independently and in parallel. The resultant protein distribution was detected by indirect immunofluorescence. Syncoilin expression was detected using the SYNC-FP antibody, whereas desmin expression was detected using the anti-desmin antibody Y-20.
Fig. 4 shows a mixed population of transfected cells. In cells transfected with syncoilin only, SYNC-FP staining was concentrated in the cytoplasm, but syncoilin failed to form filaments, as reported previously (Fig. 4A) (7). In cells positive for desmin but negative for syncoilin, cage-like IF networks could be observed (Fig. 4C). In cells containing both desmin and syncoilin, syncoilin and desmin both assumed a punctate pattern, and the two proteins co-localized in the cytoplasm. As a control, expression constructs containing the open reading frames of α-dystrobrevin and desmin were co-transfected in COS-7 cells (Fig. 4D). α-Dystrobrevin assumed a punctate cytoplasmic staining, whereas desmin assembled into a cage-like structure similar to that observed in cells singly transfected with desmin. ×63 magnification.

Fractionation of Transfected COS-7 Cells—Fractionation experiments were performed to investigate the subcellular localization of syncoilin and desmin in transfected COS-7 cells and in skeletal muscle. In COS-7 cells singly transfected with desmin, desmin was concentrated in the cytoskeletal fraction (Fig. 5A). In contrast, desmin was found in both the cytosolic and cytoskeletal fractions of co-transfected cells (Fig. 5B). These results support the observation that desmin assembled into insoluble filaments when singly transfected, whereas co-transfection of syncoilin caused the disassembly of desmin filaments into soluble units. Syncoilin, in contrast, was detected mostly in the cytosolic fraction in singly and doubly transfected cells, as is consistent with the cytoplasmic staining observed in cells singly transfected with desmin (Fig. 5, C and D). This lends support to the observation that syncoilin failed to form filaments with desmin in transfected COS-7 cells.

In skeletal muscle, desmin was detected in the cytoskeletal fraction, as is consistent with the reported insolubility of IF proteins (Fig. 5E). On the other hand, syncoilin was found mainly in the cytosolic fraction, although it was sometimes also detected in the cytoskeletal fraction (Fig. 5F).

Immunofluorescence Studies of H2K Myoblasts and Myotubes

To assess the endogenous expression pattern of syncoilin and desmin, H2K myoblasts and myotubes were immunolabeled with SYNC-FP and anti-desmin Y20 (Fig. 6A). Syncoilin could be found in all cells and assumed a punctate cytoplasmic pattern. In contrast, desmin was detected in only 40–60% of cells and assembled into a filamentous structure. Unlike the staining pattern seen in transfected COS-7 cells, desmin filaments are maintained in the presence of syncoilin.
and C). In H2K myotubes, syncoilin was again found throughout all tubes. On the other hand, desmin was only detected in a fraction of myotubes with variable intensity, and staining within each myotube was nonuniform. Desmin immunoreactivity was detected as spot-like structures, bundles of filaments, and sheets of longitudinally aligned filaments on the surface of myotubes. This may represent the integration of desmin filaments in individual myoblasts into a layer of desmin filaments at various stages of differentiation.

**DISCUSSION**

Here we describe an interaction between syncoilin and desmin, an association that may be important for linking the desmin intermediate filament network to the DAPC. We first identified syncoilin as a binding partner of α-dystrobrevin-1 and -2 using a yeast two-hybrid assay, and we classified the protein as a tentative member of the IF protein superfamily by sequence analysis (7). Based on the cellular localization and the protein structure of desmin, we speculated that syncoilin and desmin might interact. We have confirmed this hypothesis by identifying desmin as a binding partner of syncoilin. Intriguingly, syncoilin failed to form filaments when co-transfected with desmin. This suggests that syncoilin is not a component of desmin filaments but may be involved in the dynamic organization of these structures. Based on the structural functions postulated for desmin and the DAPC, we propose that syncoilin is responsible for attaching/organizing desmin filaments at the sarcolemma via the DAPC to provide structural support to muscle fibers.

Desmin is the main IF protein in muscle and is located predominantly at the neuromuscular junction, the sarcolemma, and the Z-lines. In knockout studies, muscle lacking desmin generated less stress (18) and showed increased susceptibility to damage (19), implicating desmin in the maintenance of muscle fiber integrity. Syncoilin is a member of the DAPC, which is thought to act as a mechanical bridge between the basal lamina and the actin cytoskeleton to sustain sarcolemmal integrity (3, 5, 6). By binding desmin, syncoilin may organize desmin filaments at the sarcolemma and link the extracellular matrix via the DAPC to the intermediate filament network. This role could also be extended to a pathological state, where syncoilin is up-regulated as a possible attempt to protect against muscle damage (7).

Syncoilin, desmin, and α-dystrobrevin are highly expressed at the NMJ (4, 7, 12). The loss of α-dystrobrevin leads to NMJ abnormalities, including the irregular distribution of acetylcholine receptors and a 50% reduction in the number of junctional folds, suggesting a disturbance in synaptic structure (20). Together, desmin and actin have been proposed to form submembranous support for acetylcholine receptors and to mediate the excitation of acetylcholine receptors to the sarcromeric contraction system (21). Syncoilin, by linking desmin filaments to the DAPC via α-dystrobrevin, may be involved in the maintenance of synaptic structure.

To understand the mechanism by which syncoilin functions in muscle, we performed cell transfection experiments to assess its ability to form filaments with desmin. As a type III or IV IF protein, desmin is capable of forming filaments with itself and with other IFs, such as synemin and paranemin (22, 23). Desmin successfully assembled into an IF network when transfected alone, indicating that COS-7 cells support filament formation. In contrast, syncoilin failed to form filaments when transfected on its own or when co-transfected with desmin. However, because COS-7 cells do not naturally express desmin or syncoilin, some muscle-specific cofactors necessary for heterofilament formation may be absent. Therefore, H2K myo-

**FIG. 5. Fractionation of protein extract from transfected COS-7 cells.** Protein extract from COS-7 cells transfected with desmin (A), syncoilin (C), or both (B and D) were fractionated into cytosolic (C), nuclear (Nu), and cytoskeletal fractions (CS). In cells singly transfected with desmin, desmin was concentrated in the cytoskeletal fraction (A). In co-transfected cells, a cytosolic as well as a cytoskeletal pool of desmin could be detected (B). In singly transfected and co-transfected cells, syncoilin was found predominantly in the cytosolic fraction, although it was weakly present in the other fractions (C and D). Protein extract from normal mouse skeletal muscle was similarly fractionated.

**FIG. 6. Immunofluorescence study of H2K myoblasts and myotubes.** Syncoilin and desmin expression in H2K myoblasts and myotubes was detected using SYNC-FP and Y-20. In myoblasts, syncoilin assumed a punctate cytoplasmic pattern, whereas desmin showed filamentous staining (A). In myotubes, desmin was nonuniformly distributed and was present as various desmin structures (B and C). Longitudinally aligned desmin filaments could be detected on the surface of myotubes (closed arrow). Spots of desmin immunoreactivity were also detected along the myotubes (open arrow), as were small bundles of filaments. Syncoilin was present throughout the tube and could be detected in all cells. ×100 magnification.

Myoblasts were allowed to undergo fusion for 4 days in differentiation medium, and resultant myotubes were again immunolabeled with SYNC-FP and anti-desmin Y-20 (Fig. 6, B and C).
and disassembly of vimentin and cytokeratin 5/14 filaments
IF-binding domain of plectin caused the assembly inhibition
thought to cross-link the desmin IF network to other subcellu-
ments may be a result of the perturbation of the natural ratio
ments in both myoblasts and myotubes; but unlike the COS-7
COS-7 cells, desmin filaments were maintained in the presence
of syncoilin. This suggests that the disruption of desmin filaments
malignations are both consistent with the role of syncoilin as a
heterofilaments, has also been shown to interact with
sarcolemma, the Z-lines, and the NMJ, as well as its up-regu-
Desmuslin, a protein whose gene was mutated in some patients with desmin-
malities of desmin interactors are thought to contribute to
the sarcolemma, whereas syncoilin is found at both the NMJ and the
protein is not up-regulated under pathological
cell. During the preparation of this manuscript, Mizuno et al. (36)
protein that links dystrobrevin and desmin at the sarcolemma.
This protein, desmuslin, is located at the sarco-
dermal network. Syncoilin is therefore a candidate gene for this dis-
related myopathies (33). We propose that syncoilin is respon-
sible for anchoring desmin filaments; hence, its dysfunction or
absence is likely to result in a disturbance in the desmin IF
network. Syncoilin is therefore a candidate gene for this dis-
ease. Furthermore, within these desmin inclusion bodies, dys-
trophin was detected (34, 35), giving further support to a relation-
ship between the DAPC and desmin.

In summary, we present evidence that desmin interacts with
syncoilin, and the DAPC. Based on the structural roles of desmin IFs and the DAPC, it is likely that
syncoilin contributes to the maintenance of muscle integrity by
linking the two components together. Exactly how this is
achieved is unclear at present because syncoilin does not ap-
pear to behave like other IF proteins. It is likely that syncoilin
is responsible for organizing the desmin IF network, which may
be important for the maintenance and integrity of muscle mem-
brane and the localization of the DAPC. Its localization at the
sarcolemma, the Z-lines, and the NMJ, as well as its up-regu-
lation in pathological muscle, suggests that syncoilin serves
diverse and important roles in muscle.

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