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Visions & Reflections (Minireview)

Syncoilin, an intermediate filament-like protein linked to the dystrophin associated protein complex in skeletal muscle

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Abstract. Syncoilin is a member of the intermediate filament protein family, highly expressed in skeletal and cardiac muscle. Syncoilin binds α-dystrobrevin, a component of the dystrophin associated protein complex (DAPC) located at the muscle cell membrane, and desmin, a muscle-specific intermediate filament protein, thus providing a link between the DAPC and the muscle intermediate filament network. This link may be important for muscle integrity and force transduction during contraction, a theory that is supported by the reduced force-generating capacity of muscles from syncoilin-null mice. Additionally, syncoilin is found at increased levels in the regenerating muscle fibres of patients with muscular dystrophies and mouse models of muscle disease. Therefore, syncoilin may be important for muscle regeneration in response to injury. The aims of this article are to review current knowledge about syncoilin and to discuss its possible functions in skeletal muscle.

Keywords. Syncoilin, DAPC, DGC, intermediate filament, dystrophin, muscular dystrophy, Duchenne, skeletal muscle.

Introduction

Syncoilin is a member of the intermediate filament (IF) protein family, highly expressed in striated muscle. It provides a link between the dystrophin associated protein complex (DAPC) and the desmin IF network and is upregulated in a variety of human myopathies and mouse models of muscle disease. Although the structure, localisation and key binding partners of syncoilin have been well studied, its function remains unclear. The aims of this article are to review the current knowledge about syncoilin and to discuss its possible functions in skeletal muscle.

The structure of syncoilin

Syncoilin is a 64 kDa protein, identified as a member of the IF protein family on the basis of sequence homology [1]. However, it does not form filaments either by homopolymerising or, as is the case for the majority of IFs *in vivo* (reviewed in [2]), by heteropolymerising with other IF proteins [3]. Like all IFs, syncoilin has a central rod domain made up of four coiled-coil-forming, α-helical regions separated by flexible linkers, plus an N-terminal head domain and a C-terminal tail domain, which are structurally less defined [1]. The head domain of syncoilin bears no significant homology to any other protein. The tail

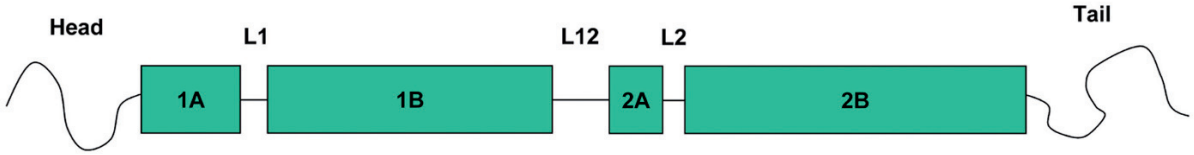

Figure 1. The consensus domain structure of an intermediate filament protein. Intermediate filament (IF) proteins are composed of four α-helical domains, helices 1A, 1B, 2A and 2B (represented by boxes), which form coiled-coils with other IF proteins. These are divided by linker regions, L1, L12 and L2 (represented by straight lines). The head and tail domains are less structurally defined, and vary in size, sequence and structure between different members of the IF protein family.

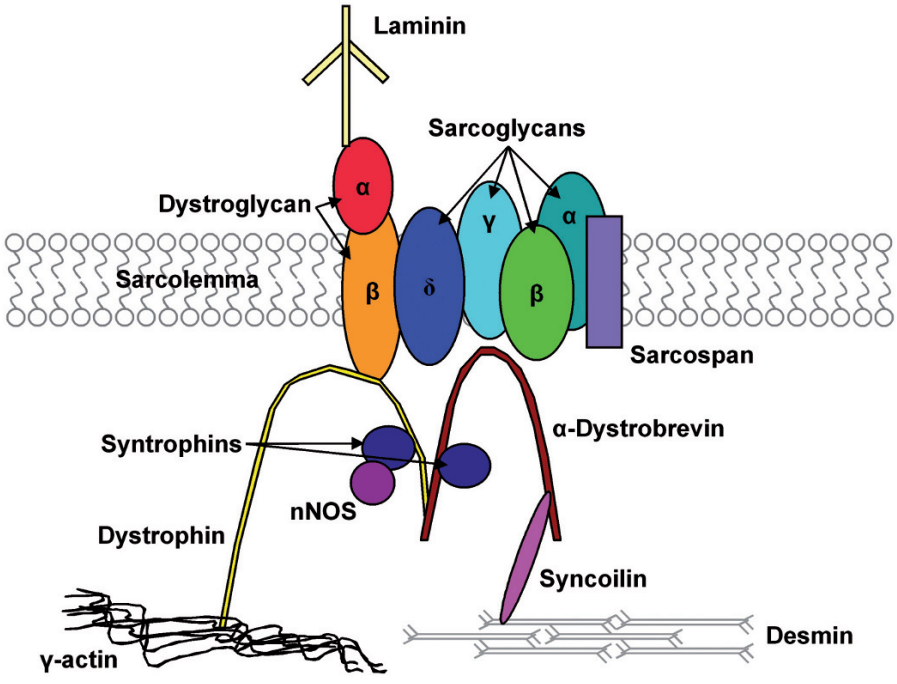

Figure 2. The dystrophin associated protein complex in skeletal muscle. The dystrophin associated protein complex (DAPC) forms a link between the extracellular matrix (ECM), through binding to laminin and other ECM molecules, and the intracellular cytoskeleton, through multiple interactions with cytoskeletal proteins. For clarity, only the well-characterised linkage between dystrophin and γ-actin and the link from α-dystrobrevin to desmin, via syncoilin, are shown. nNos, neuronal nitric oxide synthase.

domain is unusually short, which may explain in part syncoilin's lack of filament-forming ability, since tail domains of other IF proteins are important for correct filament assembly [4–6]. The consensus structure of the IF proteins is shown in Figure 1.

Syncoilin and the DAPC

The DAPC is a transmembrane complex of proteins that links the extracellular matrix to the intracellular cytoskeleton in skeletal muscle, providing mechanical reinforcement to the sarcolemma (the muscle cell membrane) and allowing efficient lateral force transduction during muscle contraction (Figure 2; reviewed in [7–9]). The DAPC is also thought to play a role in signal transduction, since it binds a number of signalling molecules, kinases and ion channels, including Grb2 [10], calmodulin [11, 12], neuronal nitric oxide synthase [13], the heterotrimeric G(s) protein [14], stress activated protein kinase 3 [15], diacylglycerol kinase-ζ [16], the SkM1 voltage-gated sodium channel [17] and the TRPC1 stretch-activated calcium channel [18]. These associations implicate the DAPC in the mediation of multiple signalling pathways, with downstream effects including regulation of the muscle blood supply, cell growth and survival, cytoskeletal reorganisation and control of intracellular calcium concentrations (reviewed in [19–23]).

Several of the muscular dystrophies are caused by mutations in components of the DAPC. The most prevalent form is Duchenne muscular dystrophy (DMD), which is caused by mutations in dystrophin. The absence of dystrophin results in loss of the entire DAPC from the sarcolemma. As a result, the muscle is unable to produce force effectively and the sarcolemma becomes vulnerable to contraction-induced damage (reviewed in [8, 24, 25]). Disruption of DAPC-mediated signalling is also thought to contribute to the pathogenesis of DMD. For example, loss of the DAPC

may be responsible for the loss of intracellular calcium homeostasis observed in dystrophic muscle, the impaired modulation of muscle blood supply during exercise in DMD patients or the generation of apoptotic signals leading to muscle degeneration (reviewed in [19–23]).

Syncoilin was originally discovered through a yeast two-hybrid screen for proteins that interact with α-dystrobrevin, another member of the DAPC [1]. A second yeast two-hybrid experiment, using syncoilin as the bait protein, identified the muscle-specific IF protein desmin as another syncoilin binding partner [3]. This was of great interest as it represented a further physical linkage between the DAPC and the cytoskeleton, in addition to the well-characterised interaction between dystrophin and actin [26–28] (Fig. 2), and suggested that syncoilin might be important for the structural integrity of muscle.

The expression pattern of syncoilin

Syncoilin is highly expressed in skeletal and cardiac muscle [1]. In skeletal muscle, syncoilin is found throughout the sarcolemma, but is enriched at the neuromuscular and myotendinous junctions (NMJ and MTJ) and around the nucleus. In the interior of the muscle fibre, syncoilin is localised to the Z-lines, but sub-cellular fractionation and immunostaining show that a proportion of syncoilin also exists in soluble form in the cytoplasm [1, 3, 29].

Interestingly, in mice null for desmin, syncoilin is lost from all of its normal cellular locations and entirely redistributed to the soluble fraction of the cell, indicating that it is dependent on desmin for its normal location and association with the cytoskeleton [29]. In contrast, syncoilin localisation is unaltered in the muscles of α-dystrobrevin-null mice, showing that the connection to the DAPC is not necessary for syncoilin stability at the sarcolemma. In fact, syncoilin is increased at the sarcolemma of α-dystrobrevin-null mice, probably as a result of their mild muscular dystrophy [29], a phenomenon discussed further below.

Syncoilin is expressed more highly in slow, oxidative fibres than in fast, glycolytic fibres [29], and therefore may contribute to the distinct characteristics of slow muscle compared to fast. For example, increased syncoilin might contribute to the differential contractile properties of slow muscle, such as decreased shortening velocity [30] and increased resistance to fatigue [31].

Syncoilin in muscle disease

Syncoilin is found at increased levels in the muscles of patients with neuromuscular disorders, including DMD, congenital muscular dystrophy (CMD) and desmin-related myopathy [32, 33]. Little is known in relation to syncoilin in CMD, but the elevation of syncoilin in DMD and desmin-related myopathy has been investigated in more depth.

Desmin-related myopathy is characterised by accumulations of desmin in the muscle fibres of patients [34], and syncoilin is found to colocalise with desmin in these accumulations [32]. Interestingly, desmin-related myopathy is not usually caused by mutations in desmin, but can be caused by mutations in another of its binding partners, αB-crystallin [35]. This suggests that syncoilin mutations might also be responsible for some instances of this disease. To date, 76 patients with desmin-related myopathy have been screened for mutations in syncoilin without any such changes being identified [36–38], but this does not exclude the possibility that rare cases exist.

Syncoilin levels are also increased in the *mdx* mouse, a model for DMD [39], and further increased in mice null for utrophin and dystrophin (dko mice) [1], which have a more severe phenotype [40]. No changes in syncoilin levels are seen in utrophin-null mice, or mice expressing a utrophin transgene on an *mdx* background [1], neither of which display any muscle disease [41, 42]. Therefore, the increase in syncoilin correlates with the degree of muscle pathology, implying that it either contributes to or compensates for the muscle damage that occurs in the dystrophic state.

Examination of the muscles of *mdx*, dko and α-dystrobrevin-null mice by immunohistochemistry shows particularly high syncoilin expression in smaller fibres with central nuclei, a sign of recent regeneration [1, 29]. Furthermore, in DMD patients, strong immunolabelling of syncoilin is observed in smaller fibres expressing neonatal myosin and neural cell adhesion molecule (NCAM) [33], which are markers of regenerating fibres. Smaller fibres are also more strongly labelled in patients with CMD [33]. Therefore, syncoilin may play a role in injury-induced muscle regeneration, a key feature of the muscular dystrophies, which would explain its increased levels in dystrophic muscle. This possibility is discussed further below.

The syncoilin-null mouse

Further evidence for the role of syncoilin in muscle comes from the recent generation of a syncoilin-null

mouse [43]. These mice display no obvious abnormalities, indicating that syncoilin is not essential for normal development. This may be because its absence can be compensated for by other proteins, such as synemin [44], plectin [45, 46] or dysbindin and myospryn [47, 48], which also link the DAPC to desmin filaments. The evolutionary advantage of this apparent redundancy in the muscle cytoarchitecture may be that loss or damage of one structural protein does not compromise the entire force-transducing network. In addition, the above-mentioned proteins, or others, may be able to compensate for any loss of signal transduction caused by the absence of syncoilin. The lack of syncoilin in the knock-out mouse does not alter the levels or localisation of desmin, α-dystrobrevin or other members of the DAPC [43]. Physiological measurements on isolated *extensor digitorum longus* (EDL) muscles show that the absence of syncoilin does not confer greater susceptibility to damage by eccentric contractions, a hallmark of dystrophin deficiency [49], in line with the fact that the DAPC is still intact and can reinforce the sarcolemma. However, syncoilin-null muscles do have a reduced capacity to generate force during isometric contractions, producing approximately 75 % of the force of normal muscles [43]. Therefore, it appears that syncoilin is important for fully efficient force transmission in skeletal muscles. Interestingly, desmin-null muscles (where syncoilin is displaced from its usual locations [29]) also display reduced force generation without increased vulnerability to damage by eccentric contractions [50]. This suggests that it may be the loss of the link between desmin and the DAPC, mediated by syncoilin, that brings about the loss of force production in syncoilin-null muscles. Despite the high levels of syncoilin expression in the heart, syncoilin-null mice have normal cardiac function and their hearts display no morphological or ultrastructural defects [43]. Therefore, syncoilin seems to be dispensable for normal heart development and function.

What is the function of syncoilin in skeletal muscle?

It appears that syncoilin is an important part of the complex network of structural proteins that form the cytoskeletal architecture of skeletal muscle and provide the mechanical strength and structural organisation necessary to bring about movement through contraction. However, the relative importance of the pool of syncoilin that links the DAPC to desmin compared to syncoilin found at other subcellular locations, such as the Z-lines and MTJ, for force generation, requires further investigation.

The association of syncoilin with both the DAPC and the desmin IF network suggests that it could play a role in the transduction of signals between these two entities. For example, it is known that IF networks are dynamic and can be modulated in response to cell signalling, particularly relating to mechanical and non-mechanical stress [51–55]. There is also some evidence that the DAPC may be involved in mechanotransduction [56–58]. Therefore, syncoilin might help to convey mechanical stress signalling from the DAPC to the desmin IF network, allowing it to respond accordingly.

In the muscles of desmin-null mice, nuclei are misaligned and appear to be uncoupled from the cytoskeleton, demonstrating a role for desmin in nuclear positioning [59]. Syncoilin is concentrated around the nucleus in normal mice [29]. However, misalignment of myonuclei has not been reported in syncoilin-null animals [43], indicating that syncoilin is dispensable for the normal positioning of nuclei in the muscle fibre.

Syncoilin might also have a specific role to play in muscle regeneration, as suggested by its increased levels in regenerating fibres [1, 29, 33]. During regeneration, activated satellite cells proliferate before fusing to form new muscle fibres, or to repair existing fibres that have been damaged (reviewed in [60]). This process is essential for the maintenance of adult muscle in the face of daily wear and tear, and to combat the extensive muscle degeneration that occurs in the muscular dystrophies. The fusion of proliferating myoblasts into multinucleated myotubes must necessarily involve widespread rearrangement of the muscle fibre cytoskeleton. For example, the cleavage of desmin by the protease m-calpain appears to be an important step in myoblast fusion [61]. Interestingly, when co-transfected with desmin in COS-7 cells, syncoilin disrupts the filamentous structures which desmin usually forms in these cells [3]. This supports the idea that syncoilin may play a role in the remodelling of the desmin network during myoblast fusion *in vivo*. Furthermore, in desmin-null mice, there is a delay in the onset of myotube formation and a longer persistence of myoblast proliferation during regeneration after graft transplantation, suggesting that desmin could be important for the switch from myoblast proliferation to fusion [62]. As syncoilin and desmin are concomitantly increased in regenerating muscle fibres in DMD patients [33], syncoilin may also be important for this switch.

The regeneration of adult muscle often recapitulates the processes of development. Therefore, if syncoilin is important for adult muscle regeneration, it may also play a role in embryonic muscle development, an area that would be of interest to investigate.

The inability of syncoilin to form filaments despite its IF protein domain structure and association with desmin suggests that its function may differ from that of other IF family members. Unlike microtubules and actin filaments, IF subunits can add to filaments laterally, as well as to the filament ends [63–65]. Therefore, a possible model for the association of syncoilin with IFs is that it attaches to the sides of filaments, and acts as a 'molecular adaptor' to allow the association of other proteins with the IF network. The link to the DAPC would be one example, but syncoilin might also serve to recruit proteins that influence the dynamics of the IF network, to link the network with other cytoskeletal elements, to act as a scaffold to assemble signalling proteins at appropriate subcellular locations or, as discussed above, to play a part in the conveyance of signals itself.

This idea of syncoilin as a 'molecular adaptor' can be related to the increased syncoilin levels seen in muscular dystrophies and other muscle diseases. Other structural proteins, such as talin and vinculin [66], α7-integrin [67], plectin [46, 68], dysbindin [47], membrane-associated filamin-2 [69] and γ-actin [70] are also found at increased levels in dystrophic muscle. Although such responses are insufficient to prevent the disease, they may serve to slow its progression and delay fatality. Increased levels of the syncoilin adaptor in muscle disease might too be a compensatory response, to strengthen the cytoskeleton or to modulate signalling in an attempt to overcome the degeneration of the muscles.

Conclusions and future directions

Syncoilin is a unique, non-filament-forming member of the intermediate filament protein family that helps link the DAPC to desmin filaments in muscle and plays a role in contractile force transmission. The evidence gathered so far suggests that syncoilin could act as a 'molecular adaptor' for IF networks, and that it may play a role in muscle regeneration. However, much work needs to be done before these ideas can be verified and the functions of syncoilin determined in greater detail. The continuing investigation of the function of syncoilin may provide important insights into the roles of IF networks in normal muscle and in muscle disease.

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