Syndecans in skeletal muscle development, regeneration and homeostasis

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Summary

Skeletal muscle is a highly dynamic tissue that can change in size in response to physiological demands and undergo successful regeneration even upon extensive injury. A population of resident stem cells, termed satellite cells, accounts for skeletal muscle plasticity, maintenance and regeneration. Mammalian satellite cells, generated from muscle precursor cells during development, are maintained quiescent in the musculature throughout a lifespan, but ready to activate, proliferate and differentiate into myocytes upon demand. Syndecans are transmembrane heparan sulfate proteoglycans expressed in muscle precursors during embryonic development and in satellite cells during postnatal life. In the last decades a number of crucial functions for syndecans in myogenesis and muscle disease have been described. Here we review the current knowledge of the multiple roles played by syndecans in the skeletal muscle of several animal models and explore future perspectives for human muscle health, with a focus on muscle aging and muscular dystrophy.

Key words: syndecans, satellite cells, myogenesis, muscular dystrophy, aging, muscle regeneration.

Introduction

Skeletal muscle fibers (myofibers) are large syncytial cells derived from the fusion of hundreds of progenitor cells during development (1). These muscle precursor cells (myoblasts) originate from the epaxial somite where, during mouse embryonic development, undifferentiated progenitors delaminate from the somite and migrate into the limb bud. Initially these progenitors proliferate and then terminally differentiate into myocytes prior to fusing with one another to form embryonic muscle fibers (2-5). A subset of these proliferating muscle progenitors are thought to be “set aside” during muscle development for the generation of satellite cells during the late stages of embryonic development (6).
Satellite cells, first described in frog muscle preparations (7), are the skeletal muscle stem cells (8,9) in all vertebrates, including humans (10). Satellite cells spend the vast majority of their lifespan mitotically quiescent, located within a specialized anatomic niche between the plasma membrane of the myofiber and the surrounding basal lamina (7). Each myofiber harbors 7-27 satellite cells, depending on the fiber type (11). In response to stimuli such as exercise or injury, satellite cells are activated, express the myogenic master gene MyoD and re-enter the cell cycle; activated and proliferating MyoD+ satellite cells are termed myoblasts. After one or more rounds of proliferation, myoblasts exit the cell cycle and terminally differentiate into myocytes, which express muscle contractile proteins and fuse either one to another to form new myofibers or to pre-existing damaged myofibers to repair them (12).
During embryonic development and in postnatal life, a family of transmembrane heparan sulfate proteoglycans (HSPGs) called syndecans have emerged as key regulators of skeletal muscle formation and maintenance. In this review we discuss the role played by syndecans in skeletal muscle development, maintenance and regeneration in healthy and diseased or aging organisms. We will then highlight future perspective for human muscle health that can be inferred based on studies carried out on animal models.

Syndecan structure

Syndecans are transmembrane HSPGs, complex molecules comprising a core protein that covalently links one or more long, linear carbohydrate chains, the glycosaminoglycan (GAG) chains (13). Syndecans are conserved in all metazoans (14). The core protein structure is shared by all syndecans across large evolutionary distances, from the single syndecan expressed in invertebrates to the four different syndecans expressed in vertebrate organisms. However, the specific sequence can vary considerably across gene homologues and across species (14).
The ectodomain is the most variable region of the syndecan core protein containing a N-terminal signal peptide and several attachment sites for heparan sulfate chains. Additionally, syndecan-1 and syndecan-3 also contain attachment

sites for chondroitin sulfate chains (15). The syndecan ectodomain also contains at least one proteolytic cleavage site close to the transmembrane domain that is recognized by metalloproteinases (16). Syndecan shedding has an important regulatory function since shed, soluble ectodomains can function as paracrine or autocrine effectors or competitors (16). Moreover, ectodomain shedding is a way to quickly stop the processes that transmembrane syndecans take part in (16).

The transmembrane domain is a conserved single hydrophobic region, while the short intracellular domain contains three regions where a variable intermediate region (V) separates two highly conserved regions, C1 and C2, with C1 being essentially identical in all syndecans (17).

Heparan sulfate (HS) contains a linear backbone composed by repeating sequences of glucuronic acid and N-acetyl-glucosamine disaccharide units. In HSPGs, each HS chain is attached through a xylose-galactose-galactose-uronic acid tetrasaccharide linker to serine residues on the core protein (15). HS is synthesized in the Golgi where a complex set of enzymes catalyzes not only the addition of the linker and each alternating saccharide unit, but also subsequent sugar modifications, which include C-5 epimerization of glucuronic acid that yields iduronic acid, replacement of N-acetylation with N-sulfation at GlcNAc residues and three different O-sulfations: 2-O-sulfation, 3-O-sulfation and 6-O-sulfation (13). HS contains a variable number of disaccharide units (up to 200) with highly sulfated domains alternating with less sulfated domains. It appears that specificity of heparan sulfate for its interactors is determined mainly within the highly sulfated domains. Moreover, it has been shown that one single HS chain can bind multiple interactors simultaneously, thus yielding complex supramolecular structures such as in the case of FGF and FGF receptors (18). The highly variable number of repeating disaccharide units together with the large number and assortment of saccharide modifications yields an incredibly high number of possible “sequences” of functional units, which is why HS is considered the biomolecule with the highest degree of diversity (19).

Chondroitin sulfate (CS) chains have a backbone composed by repeating glucuronic acid and N-acetyl-galactosamine disaccharide units attached to the core protein through the same tetrasaccharide linker that connects HS to the core protein. As opposed to HS, CS chains contain a less diverse range of modifications and these are more equally distributed along the chain (13).

Syndecans in skeletal muscle development

Syndecan involvement in skeletal muscle development has been investigated in flies, turkeys and mice (20-23).

During *Drosophila* development, the single syndecan is expressed in muscle fibers and appears to be involved in motor-axon guidance by acting as a receptor for the neural receptor tyrosine phosphatase (RPTP) LAR (22). Thus, *Drosophila* syndecan controls muscle innervation during development and therefore regulates the onset of muscle functional maturation. Whether *Drosophila* syndecan is also involved directly in regulating embryonic myofiber formation, is unknown.

The role of syndecans in vertebrate muscle development has been studied in mice and birds (20,24). Developing mouse muscles express syndecan-1, syndecan-3 and syndecan-4 with similar topological distributions, but different temporal regulation (20,21). Northern and Western blot analyses of syndecan-1, syndecan-3 and syndecan-4 mRNA and protein, respectively, show that syndecan-1 protein peaks prior to other syndecans, around E12.5, then rapidly decreases and is completely absent by P2 (20). In contrast, syndecan-3 and syndecan-4 peak around E14.5 and E13.5 respectively, but then decrease much more slowly and are still expressed in newborn and adult mice (20,25). Expression of syndecan-1, syndecan-3 and syndecan-4 in embryonic muscle is localized to both myoblasts and myofibers. While syndecan-1 is not detected in postnatal muscle, syndecan-3 and syndecan-4 proteins are restricted to satellite cells and possibly vascular cells (21).

In embryonic turkey muscle, distribution of syndecan expression between E14 and E24 is regulated in a similar pattern as in mice, peaking between E14 (syndecan-3), E16 (syndecan-2) and E18 (syndecan-4), followed by a decline at later time points (E22-E24). Syndecan-2, 3 and 4 expression is presumably restricted to satellite cells in postnatal turkey muscle (23).

Important roles for syndecans in muscle development were confirmed in turkey embryonic pectoralis major muscle at different developmental stages (E14 - E24) derived from either a high body weight genetically selected line (F line) or a low body weight line (RBC2 line). In this study, Liu et al., found that the F line (high body weight) turkey muscle has higher levels of syndecan-2, syndecan-3 and syndecan-4 than the RBC2 line (low body weight) turkey muscle, supporting a key role for syndecans in the regulation of muscle development and size (23).

Syndecans in skeletal muscle maintenance and regeneration

The hypothesis that HSPGs, such as syndecans, are involved in myogenesis could have been already inferred when a key role for HS in growth factor signaling in myoblasts was described (26,27). Subsequent studies from Brandan and colleagues showed a role for specific HSPGs in myogenic differentiation using the C2C12 myoblast cell line (28-33). Shortly after this group showed that gene expression levels and protein levels of a number of HSPGs were regulated *in vivo* during injury-induced regeneration in mouse limb muscles (34). The only two syndecans identified by Casar et al. that appeared to be expressed in regenerating muscle were syndecan-3 and syndecan-4 (34). Indeed, Cornelison et al. had previously shown that syndecan-3 and syndecan-4 are the only two syndecans detectable by immunofluorescence in postnatal mouse skeletal muscle, co-localizing with markers of satellite cells (21). The time course of syndecan-3 and syndecan-4 expression

during muscle regeneration together with the observation that their expression was restricted to satellite cells, led to the hypothesis that these two syndecans played a role in satellite cell-mediated muscle regeneration and prompted further analyses of the muscle phenotypes of *Sdc3*$^{-/-}$ and *Sdc4*$^{-/-}$ mice (35).

Though syndecan-3 and syndecan-4 are both expressed in quiescent satellite cells expression of these HSPGs in activated, proliferating and differentiating satellite cells during injury-induced regeneration is distinct (Tab. 1) and (34,36), in fact in 2004 Cornelison et al. described distinct roles for syndecan-3 and syndecan-4 in satellite cell-mediated muscle regeneration (35). *Sdc4*$^{-/-}$ satellite cells show impaired activation, leading to impaired regeneration upon $BaCl_2$-induced injury (35). In contrast, *Sdc3*$^{-/-}$ satellite cells exhibit the opposite phenotype: impaired quiescence maintenance and renewal with a shift of the quiescent satellite cell pool toward a pool of transit-amplifying myoblasts (35,37).

A detailed inspection of the HSPG phenotype of quiescent and injury-activated satellite cells that our laboratory has recently performed, reveals that the most significant changes occurring in activated satellite cells *in vivo* is a general down-regulation of HSPGs (Tab. 1) accompanied by a decline in enzymes involved in GAG synthesis and modification (Tab. 2). Only Syndecan-4 and two enzymes involved in HS sulfation are upregulated in response to injury (Tab. 1 and 2). Thus, these observations suggest that the heparanome of quiescent satellite cells may be responsible for coordinating signals in the satellite cell niche that are responsible for maintaining satellite cell quiescence. Interestingly, we recently showed that *Sdc3*$^{-/-}$ satellite cells fail to maintain quiescence and to renew (or re-acquire) a quiescent state following muscle injury (37). This observation, in addition to the observation that syndecan-3 is involved in the regulation of several signaling pathways (Pisconti et al., unpublished data) suggests that syndecan-3 may act as a master regulator of the satellite cell signaling network that is associated with quiescence. In contrast, syndecan-4 may be the only satellite cell-specific HSPG involved in satellite cell activation and cell cycle entry.

Molecular mechanisms of syndecan function in skeletal muscle

Syndecans are complex molecules that have the potential to signal simultaneously through multiple pathways (38). Through both core protein and GAG chains each syndecan can interact with a large number of molecules, and the list of syndecan interactors is continuously increasing

Proteoglycan - gene name	Abbreviation	0h - 12h	0h - 24h	12h - 24h	24h - 48h	0h - 48h
CD44 antigen	CD44			7.85		
Syndecan 4	Sdc4			10.42		11.68
Chondroitin sulfate proteoglycan 4 (NG2)	Cspg4					-6.91
Glypican 4	Gpc4	-3.52	-3.56			-3.66
Glypican 6	Gpc6		-2.11			-2.20
Sparc/osteonectin, cwcv and kazal-like domains proteoglycan 2	Spock2			-2.26		
Syndecan 1	Sdc1	-4.00				-4.50
Syndecan 2	Sdc2	-9.97	-12.47			-10.58
Thrombomodulin	Thbd				-5.77	

Table 1. *Many proteoglycan transcripts are downregulated upon satellite cell activation.* Wild type satellite cells were isolated from uninjured and injured tibialis anterior muscles at 12, 24 and 48 h following BaCl2-induced injury, total mRNA extracted and hybridized on Affymetrix gene chips to perform global gene expression analysis. The Table shows all proteoglycans that changed 2-fold or greater with a p-value < 0.01 between time points as indicated. Green = downregulated transcripts. Red = upregulated transcripts.

Enzyme - gene name	Abbreviation	0h - 12h	0h - 24h	12h - 24h	24h - 48h	0h - 48h
Exotoses (multiple)-like 2	Extl2				10.81	
Heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1	Hs3st3b1	2.43	2.36			
N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1	Ndst1	-3.01	-3.28			6.50
Exostoses (multiple)-like 3	Extl3		-4.54		4.24	
Exostoses (multiple) 1	Ext1	-4.63	-3.24			-4.55
Glucuronyl C5-epimerase	Glce	-12.00	-14.12			-8.94
Heparan sulfate 2-O-sulfotransferase 1	Hs2st1	-2.13				-2.22
3'-phosphoadenosine 5'-phosphosulfate synthase 2*	PAPSS2*	-6.87	-5.92			
Sulfatase 1	Sulf1	-5.10	-5.25			-12.11
Sulfatase 2	Sulf2	-29.94				

*PAPSS2 is not directly in the biosynthesis pathway but is directly downstream as it controls how much active sulfate is available to the enzymes

Table 2. *Proteoglycan biosynthesis and modifying enzymes are regulated upon satellite cell activation.* Wild type satellite cells were isolated from uninjured and injured tibialis anterior muscles at 12, 24 and 48 h following BaCl2-induced injury, total mRNA extracted and hybridized on Affymetrix gene chips to perform global gene expression analysis. The Table shows all enzymes that changed 2-fold or greater with a p-value < 0.01 between time points as indicated. Green = downregulated transcripts. Yellow = transcripts variably regulated over time course. Red = upregulated transcripts.

(38). Decoration of HSPG core proteins with GAG chains and subsequent saccharide modifications may be more cell type-specific than core protein-specific. In other words, the same core protein tends to receive different GAG chains when expressed in different cell types, or under different physiological states, with this depending mainly on the set of GAG biosynthetic enzymes expressed in each cell type (39,40). The opposite case, that different core proteins receive similar GAG chains when expressed in the same cell type has been proposed in the context of fibroblast adhesion, where different membrane bound HSPGs bear GAG chains that are different in length but similar in sulfation pattern and capability to bind fibronectin (41). However, Tumova et al. did observe subtle differences in HS structure present on different core proteins expressed in the same cell type and the fact that the only function tested by Tumova et al., fibronectin binding, did not change significantly across the different core proteins examined, does not exclude that other functions that were not tested (e.g. growth factor binding) could change accordingly with the difference in HS structure observed. In support of this hypothesis it has been shown that even small differences in HS structure can dramatically affect FGF binding (42) and function (43). Thus, the possibility that different core proteins receive different GAG chains with different biological functions when expressed in the same cell type is still open.

In postnatal mammalian skeletal muscle the only two syndecan proteins detected are syndecan-3 and syndecan-4 (21), which are expressed in satellite cells and appear to control muscle homeostasis through distinct mechanisms (35,37).

Syndecan-3 is the largest syndecan in mammals, harboring both HS and CS chains (17,44,45). In mouse satellite cells, syndecan-3 is found in a complex with Notch1 and promotes TACE-mediated cleavage of Notch, allowing for Notch signal transduction into satellite cells (37). In the absence of syndecan-3, Notch processing upon ligand binding is dramatically reduced as is generation of the Notch intracellular domain and subsequent induction of Notch target genes (37). As a consequence of reduced Notch signaling, *Sdc3*$^{-/-}$ satellite cells proliferate more slowly than wild type cells and fail to maintain or to return to a quiescent state (37). The resulting phenotype is intriguing: *Sdc3*$^{-/-}$ injured muscles retain full regenerative capacity and undergo progressive myofiber size increase over time despite showing a dramatic loss of satellite cells (37). A possible hypothesis to explain this paradoxical phenotype has been proposed (37): loss of syndecan-3 impairs satellite cell capacity to enter a quiescent state without affecting their ability to differentiate. Thus, a shift in the satellite cell population from a quiescent pool to an activated, proliferating and differentiating pool over time leads to myofiber hypertrophy and depletion of the quiescent satellite cell pool (37). Although loss of quiescence but not differentiation can be explained by loss of Notch signaling, this cannot explain how *Sdc3*$^{-/-}$ myoblasts remain proliferative for a long time. It is possible that other signaling pathways regulated by syndecan-3 in satellite cells compensate for loss of Notch signaling to maintain *Sdc3*$^{-/-}$ myoblasts in a proliferative cycle. Indeed, syndecan-3 also regulates FGF and HGF signaling, though the molecular mechanisms involved are unknown (30,35). In *Sdc3*$^{-/-}$ satellite cells Notch signaling is decreased while FGF and HGF signaling are increased (35) and may account for the observed maintenance of a population of proliferating myoblasts. Whether the core protein or the GAG chains of syndecan-3 are the main mediators of syndecan-3 function in satellite cells and myoblasts is unknown, however both are required to rescue the Notch signaling phenotype in *Sdc3*$^{-/-}$ myoblasts (37).

Syndecan-4 is the smallest syndecan, but the best studied in myoblasts as well as in other systems (46). In mouse muscle, syndecan-4 plays a key role in mediating satellite cell activation in response to injury (35). Though the molecular mechanisms underlying syndecan-4 function in mouse satellite cells are largely unknown, it has been hypothesized that syndecan-4 HS chains are involved in the regulation of FGF and HGF signaling in proliferating satellite cells (35). In the absence of syndecan-4, both FGF and HGF signaling are impaired, but can be rescued by heparin treatment (35). However, a direct mechanistic analysis of syndecan-4 function in mouse satellite cells is missing. In contrast, a significant effort has been made to understand whether a functional interaction between syndecan-4 and FGF2 exists in turkey satellite cells (47,48). This hypothesis is reasonable, since (a) syndecan-4 is involved in FGF2 signaling in other systems outside the musculature, (b) both FGF2 treatment and syndecan-4 ectopic expression in primary satellite cells lead to differentiation inhibition (47). However, genetic analysis revealed that in turkey satellite cells syndecan-4, with or without GAG chains, promotes proliferation and inhibits differentiation in an FGF2-independent manner (47-49).

Syndecan-4 is also expressed in young myotubes prior to myofiber growth and final maturation (21). An intriguing recent finding shows that syndecan-4 protein, along with β1-integrin, localizes in costamers of cultured rat myotubes and is regulated by electrical activity (50). Denervation of rat tibialis anterior muscles or treatment of cultured myotubes with tetrodotoxin induce syndecan-4 and β1-integrin downregulation and are associated with reduced myotube adhesion (50).

Lastly, a role for syndecan-4 in myoblast migration has been hypothesized, however a detailed analysis is missing.

Heparan sulfate and ***chondroitin sulfate*** are the two types of GAG chains covalently attached to syndecan core proteins (15). The role of HS and CS in muscle function and myogenesis has been studied irrespectively of which core proteins were attached to them (21,26,51-58). Understanding how GAGs function and signal is complicated and fascinating since: (1) the saccharide sequence of GAG chains is not template driven as is the amino acid sequence of proteins, but is the final result of multiple enzymes active simultaneously in a cell; (2) the signal mediated through GAG chains appears to be an “analog” signal where the entire pattern of saccharide and sulfated domains present at a given time in a given microdomain of the cell, can affect multiple functions simultaneously, as opposed to the “digital” type of signal driven by canonical protein-protein interactions such as ligand-receptor, kinase-substrate, etc;

and, (3) despite its generally "analog" nature, GAG interactors often exhibit high specificity for distinct oligosaccharide sequences.

Both HS and CS are involved in muscle precursor proliferation and differentiation, with highly sulfated HS generally promoting proliferation and CS generally promoting differentiation (26,34,51,52,55,57,59,60), though exceptions to this general trend have been described (58,61). Unexpectedly, we have recently determined that satellite cell activation induces downregulation of several proteoglycans (PGs) and GAG biosynthesis enzymes, suggesting a key role for PGs present in the satellite cell niche in maintaining satellite cells in a quiescent state (Tab. 1 and Tab. 2).

Interesting results have recently arisen from the study of knockout mice lacking expression of one or more enzymes involved in GAG biosynthesis. For example the satellite cell phenotype observed in *Sulf1*$^{-/-}$;*Sulf2*$^{-/-}$ double knockout mice appears the opposite of the phenotype observed in *Sdc3*$^{-/-}$ mice (37,57). Sulfs are extracellular enzymes that remove sulfate groups from HSPGs (heparan sulfate endosulfatases) (62). Based on these results it is plausible to hypothesize that loss of one HSPG (such as syndecan-3) leads to a general rearrangement of the satellite cell glycocalyx resulting in an overall reduction in HS on the satellite cell surface. Vice-versa, loss of two extracellular sulfatases is expected to cause a general increase in sulfated HS on the satellite cell surface, which may explain why the *Sdc3*$^{-/-}$ muscle satellite cell phenotype appears opposite when compared to the *Sulf1*$^{-/-}$;*Sulf2*$^{-/-}$ phenotype (37,57). Moreover, loss of one HSPG may also indirectly affect the level of decoration and amount of sulfation of other HSPGs by disrupting the normal distribution of GAG biosynthesis enzymes across several core proteins and by altering the normal balance between positive and negative feedback loops in each biosynthetic pathway.

Syndecans in aged and diseased skeletal muscle

Muscular dystrophy is a family of genetic disorders characterized by muscle weakness, chronic inflammation, fibrosis and eventually muscle loss (63). Although mutations in more than 20 different genes have been found that cause a clinical phenotype classified as muscular dystrophy, some histopathological features are shared by the vast majority of muscular dystrophies, including alterations to the satellite cell niche that are associated with exhaustion of satellite cell regenerative capacity (63).

The level of HSPGs in muscles of dystrophic patients or animals is generally increased (33,54,64-68), suggesting a pathogenic role for HS and HSPGs in muscular dystrophy. In particular, syndecan-3 was augmented in Duchenne patients (33) and this finding, together with the finding that *mdx* satellite cells have increased levels of HS and CS and increased responsiveness to FGF (54), provided impetus to study the role of syndecan-3 in dystrophinopathies such as Duchenne muscular dystrophy (DMD). Indeed, our laboratory has recently observed a possible pathogenic role for syndecan-3 in a mouse model of DMD, although this work is still in progress as we write.

Aging of human subjects is often associated with frailty, sarcopenia and impaired muscle regeneration, representing a major public health problem in modern societies where the average lifespan has increased (69). As in muscular dystrophy, also in aging the prevailing hypothesis to explain loss of regenerative capacity is the exhaustion of satellite cell numbers or function, although the underlying cellular and molecular mechanisms are a matter of debate (70-75). If progressive impairment of satellite cell regenerative capacity is a major cause of age-related muscle weakness and loss, it is reasonable to hypothesize a key pathogenic role for the aging satellite cell niche, which is characterized by reduced vascularization and increased fibrosis and adipogenesis (76,77). Several signaling pathways have been found altered in aging satellite cells *in vivo* (71,78,79). Moreover, it has been shown through parabiosis experiments that a "young environment" can rescue age-related muscle regeneration defect in mice (72). Our laboratory has recently shown that when young satellite cells are transplanted into young hosts together with their native niche (the myofiber), the transplanted muscle retains full regenerative capacity as the recipient animal ages as opposed to its non-transplanted contralateral, which undergoes the normal process of age-related loss of muscle mass and function (80). This prevention of muscle aging observed in transplanted muscles is entirely supported by donor-derived satellite cells, which remain viable in the host muscle throughout the mouse lifespan (80). When the donor cells (myofiber + associated satellite cells) where isolated from *Sdc4*$^{-/-}$ mice, this anti-aging effect was not observed, pointing out to syndecan-4 as a crucial component of the satellite cell niche (80).

Perspective for human health

Only in the last decade have the HSPG and muscle biology communities begun to appreciate the importance of syndecans in skeletal muscle development and regeneration and therefore it is not surprising that only a few studies in humans are yet available. However, studies in mice and other model organisms show promising results that will certainly inspire more human research.

Of particular interest are the findings concerning muscle injury, muscular dystrophy and aging. While there is no information on the role of syndecans during muscle injury and aging in humans, it has been shown that expression levels of some proteoglycans, including syndecan-3, is augmented in Duchenne muscular dystrophy patients (33,64,67). This observation, in conjunction with our recent observations made in *Sdc3*$^{-/-}$ and dystrophic mice suggests that syndecans may be promising therapeutic targets.

The satellite cell niche is altered in dystrophic muscles, possibly due to continuous myofiber damage and leakage, myofiber necrosis and chronic inflammation, which in turn lead to extracellular matrix remodeling (81). In this context, targeting specific components of the niche, such as syndecans, may represent a potential therapeutic strategy for enhanc-

ing muscle regeneration and slowing disease progression. Although a therapy that enhances muscle regeneration is not expected to be curative for muscular dystrophy, it is reasonable to hypothesize that enhancing regeneration would greatly improve the lifestyle of dystrophic patients (82). Additionally, therapies aimed at improving muscle regeneration are also expected to increase the efficacy of stem cell and gene therapies, either by promoting exogenous stem cell contribution to host myofiber or by favoring contribution from transduced endogenous satellite cells.

Finally, a potential role for syndecans in human muscle health that has not been sufficiently explored is the use of syndecans as viral receptors for gene therapy. HS is involved in many viral infection processes acting as a receptor or co-receptor for viral particles (83). For example, infection of muscle fibers with herpes simplex virus type 1 (HSV-1) is mediated by HS, although inhibited by other unidentified ECM components (84). This is a field that has the potential to yield interesting results in the future, as the unique expression of syndecan-3 and syndecan-4 is satellite cells could be used, for example, to target viral vectors specifically to satellite cells.

In the last century the study of HSPGs in the musculoskeletal and other systems has produced a whole new level of understanding of cell adhesion, cell signaling and cell differentiation and provided essential tools for the protection of human health. For example, heparin, a highly sulfated heparan sulfate, is one of the most widely used therapeutic agents worldwide. Future studies aimed at identifying roles for syndecans in human healthy and diseased muscle in conjunction with a detailed characterization of the signaling pathways and molecular networks controlled by syndecans, are expected to contribute significantly to our understanding of muscle biology and our ability to treat muscle disorders.

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