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REVIEWS

The role of satellite and other functional cell types in muscle repair and regeneration

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Abstract

Skeletal muscles play essential roles in physiological processes, including motor function, energy hemostasis, and respiration. Skeletal muscles also have the capacity to regenerate after injury. Regeneration of skeletal muscle is an extremely complex biological process, which involves multiple cell types. Skeletal muscle stem cells (also known as satellite cells; SCs) are crucial for the development, growth, maintenance and repair of the skeletal muscle. Cell fates and function have been extensively studied in the context of skeletal muscle regeneration. In addition to SCs, other cell types, such as fibro-adipogenic precursors (FAPs), endothelial cells, fibroblasts, pericytes and certain immune cells, play important regulatory roles during skeletal muscle regeneration. In this review, we summarize and discuss the current research progress on the different cell types and their respective functions in skeletal muscle regeneration and repair.

Keywords Muscle regeneration · Satellite cell · Fibro-adipogenic precursor · Endothelial cell · Immune cell · Lymphocyte

Introduction

Skeletal muscles play important roles in controlling physical activity, including the retention of postural control and locomotion (Iizuka et al. 2014). Skeletal muscles make up more than 35% of the adult body, and contain 50–75% of all body proteins (Janssen et al. 2014). Skeletal muscles are composed of thousands of contractile muscle cells (also referred to as muscle fibers) and are covered by connective tissue. During embryonic and fetal development, muscle stem cells fuse together to form muscle fibers. Each muscle fiber is approximately 100 µm in diameter and 1 cm in length, and is wrapped in a cell membrane or sarcolemma. Each contractile unit of muscle consists of sarcomeres, which are composed of thin actin filaments and thicker myosin filaments. There are many proteins in the sarcolemma that are closely related to the internal myofilament. Once these proteins are absent due to pathological conditions, or in other cases, such as acute injury, chronic muscle disease and experimental models, the sarcolemma will be destroyed and cause muscle weakness and atrophy. It has been reported that the types of injury (acute versus chronic, experimental models (which) versus pathogenic injury etc.) can change the satellite cell/immune response (Hardy et al. 2016). For example, freeze injury kills all cells in the area, but leaves the physical components largely intact, while crush injury more selectively affects structure (Hardy et al. 2016). In addition, Duchenne and Becker muscular dystrophies are mainly caused by the absence of dystrophin, which is coded by the DMD gene (Thomas 2013).

Skeletal muscles can regenerate in response to injury, and with the evolution or adaptation of living organisms (Blau et al. 2015). The regeneration and remodeling of skeletal muscles after injury are extremely complex biological processes, in which skeletal muscle stem cells (also known as satellite cells; SCs) are involved. As a result, the function and regulation of muscle SCs have been extensively investigated (Wang and Rudnicki 2011; Relaix and Zammit 2012; Sousa-Victor et al. 2015; Baghdadi and Tajbakhsh 2018; Fukada 2018). In addition to SCs, several other cell types, such as fibro-adipogenic precursors (FAPs), endothelial cells and immune cells also participate in this regenerative process (Ceafalan et al. 2014; Wosczyna and Rando 2018). In this review, we discuss the cell types and their respective

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functions in skeletal muscle regeneration. The goal of this review is to outline the intricate relationship between muscle stem cells and immune cells in order to provide a framework for further investigations into their function in muscle regeneration.

Skeletal muscle SCs

Skeletal muscle SCs are indispensable for postnatal skeletal muscle growth, maintenance, and repair (Mauro 1961; Collins et al. 2005; Kuang et al. 2006; Wosczyna and Rando 2018). SCs are the primary cell type involved in skeletal muscle regeneration (Relaix and Zammit 2012). SCs are heterogeneous and exist between the sarcolemma and the basal lamina of muscle fibers (Collins et al. 2005; Sacco et al. 2008; Cheung and Rando 2013; Almada and Wagers 2016; Quarta et al. 2016). In mature resting muscles, SCs are predominantly quiescent (Brack and Rando 2012). After injury or degeneration, SCs will be activated, re-enter the cell cycle and repair the injured area (Zammit et al. 2004; Kuang et al. 2006; Sacco et al. 2008; Almada and Wagers 2016). The activated SCs will undergo self-renewal, proliferation, differentiation, and fusion, and subsequently form new muscle fibers (Zammit et al. 2004; von Maltzahn et al. 2013) (Fig. 1).

Studies have shown that Paired box protein 7 (Pax7) is an important regulator of the SCs pool (Seale et al. 2000, 2004). A subset of SCs also expresses Pax3, which is a paralog of Pax7 (Relaix et al. 2006; Buckingham and Relaix 2007). The myogenic determination and differentiation of SCs are controlled by myogenic regulatory factors (MRFs), such as myogenic factor 5 (Myf5), myogenic differentiation (MyoD), myogenic regulatory factor 4 (Mrf4), and myogenin (Perry and Rudnick 2000). Myf5 is expressed before the adoption of the myogenic fate and can induce the expression of MyoD to drive SCs to the myogenic lineage. Myogenin and Mrf4 are expressed later and are crucial for terminal differentiation. Normal SCs typically express Pax7, and SCs also express Myf5 (Kuang et al. 2006). Upon injury, SCs are activated and the expression of Myf5 and MyoD rapidly increase (Cornelison and Wold 1997). Pax7 can directly regulate Myf5 and MyoD expression (Parise et al. 2008). Then, myogenic cells enter the final differentiation stage and fuse with existing myofibers to form new myofibers, ultimately expressing myogenin, MRF4 and other mature muscle-specific genes including muscle creatine kinase (MCK) and myosin heavy chains (MyHC). Therefore, the different stages of SCs differentiation can be distinguished by the expression of Pax7, MyoD, and MyoG as follows: $Pax7^{+}MyoD^{-}$ (quiescence/self-renewal), $Pax7^{+}MyoD^{+}$ (proliferation) and $Pax7^{-}MyoD^{+}MyoG^{+}$ (differentiation) (Liu

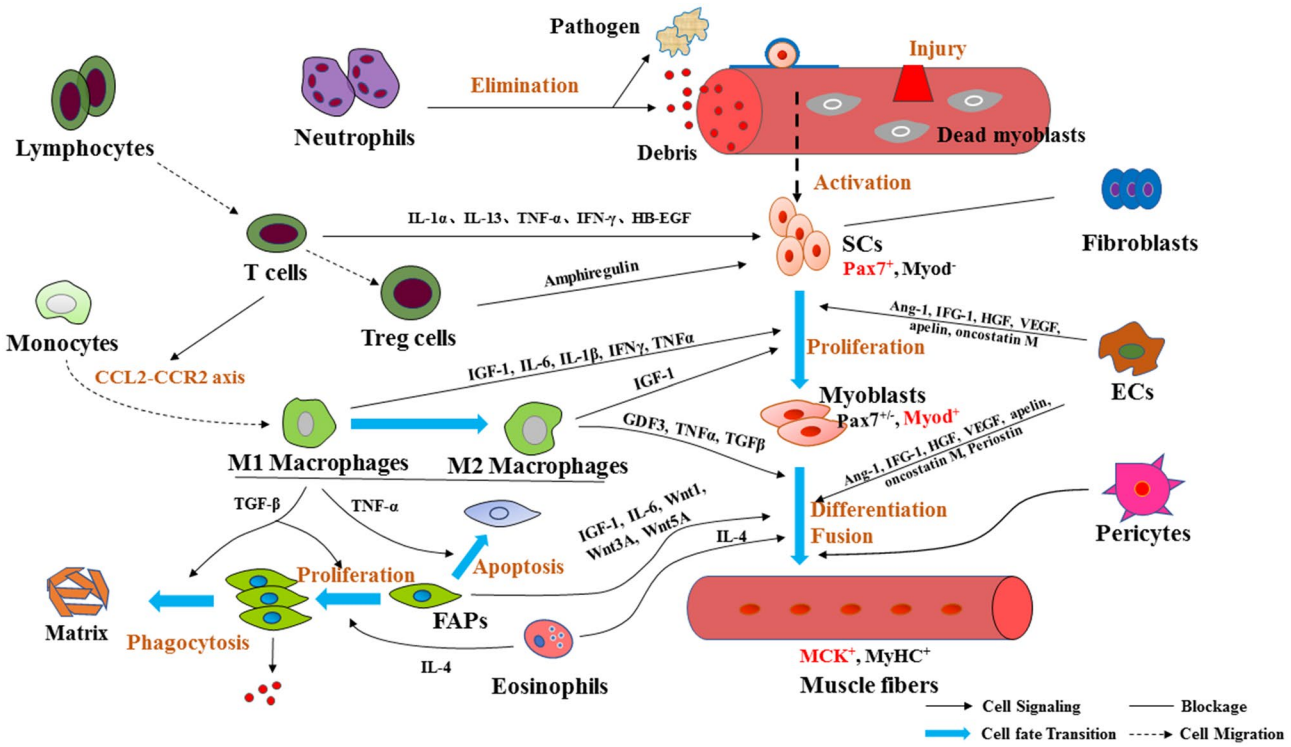

Fig. 1 Multiple *cell* types contribute to skeletal muscle regeneration. *SCs* satellite cells, *FAPs* fibro-adipogenic precursor cells, *ECs* endothelial cells

et al. 2012; Shan et al. 2014). Therefore, SCs are responsible for skeletal muscle repair and regeneration (Fig. 1).

Previous studies have suggested that the lack of SCs in mice resulted in failed regeneration (Fry et al. 2015) and severe muscle function disorders (Seale et al. 2000, 2004; Kuang et al. 2006). In mdx-nude hosts, the number of SCs decrease during aging, resulting in impaired skeletal muscle regeneration (Collins et al. 2005; Motohashi and Asakura 2014). Deteriorating satellite cells can lead to a series of diseases, such as Duchenne muscular dystrophy (DMD) (Dumont et al. 2015). Therefore, regulation of the number and function of SCs is important for postnatal skeletal muscle regeneration. Several molecular factors and signaling pathways that regulate SC' fate and skeletal muscle regeneration have been identified, such as notch1 (Conboy et al. 2003; Wen et al. 2012; Bi et al. 2016; Shan et al. 2017b), Wnt (Polesskaya et al. 2003; Brack et al. 2007; Girardi and Le Grand 2018), phosphatase and tensin homolog (Pten) (Hu et al. 2010; Yue et al. 2016, 2017), and transforming growth factor-beta (TGF-β) (Kim and Lee 2017), liver kinase B 1 (Lkb1), (Shan et al. 2014, 2017a) and insulin-like growth factor 1 (IGF1) (Schiaffino and Mammucari 2011). However, more studies are needed to comprehensively investigate the molecular mechanisms that regulate SCs and muscle regeneration.

Fibro/adipogenic progenitors (FAPs)

FAPs are multipotent progenitor cells that reside in skeletal muscles. FAPs are PDGFRα- or Sca1-positive cells that have similar functional and phenotypic characteristics as mesenchymal stem cells and are associated with ectopic fat deposition and fibrosis in skeletal muscles (Joe et al. 2010). Although not directly involved in the generation of myofibers, FAPs improve the performance of satellite cells and promote the differentiation of primary myogenic progenitors and facilitate myogenesis (Joe et al. 2010; Uezumi et al. 2010; Heredia et al. 2013; Mozzetta et al. 2013). FAPs plunk for SC differentiation and create a regenerative milieu for extracellular matrix remodeling and correct cellular components (Juban and Chazaud 2017a; Wosczyna and Rando 2018). FAPs provide an environment that promotes myogenic differentiation and increases the proportion of terminally differentiated muscle stem cells in a crosstalk perspective (Joe et al. 2010). In this environment, several active factors produced by FAPs can enhance myoblast differentiation, including insulin-like growth factor-1 (IGF-1), interleukin-6 (IL-6), Wnt1, Wnt3A, and Wnt5A (Joe et al. 2010) (Fig. 1).

Another significant facet of FAPs that can contribute to muscle regenerative function is their ability to interact with infiltrating immune cells. Recent data have shown that cytokines secreted by inflammatory macrophages can modulate FAPs (Lemos et al. 2015). After FAPs go through serial proliferation, tumor necrosis factorα (TNFα) released by macrophages target FAPs for apoptosis. In addition, studies have demonstrated that FAPs can clear necrotic residues by means of phagocytosis (Heredia et al. 2013). Hence, FAPs are indispensable cells in regeneration and play a vital role in maintaining a regenerative environment (Fig. 1).

Immune cells

Macrophages

Immune cell infiltration and inflammation are the most immediate cellular responses to muscle injury. Macrophages are multi-functional cells that are closely related to the pro-inflammatory and recovery stages of tissue repair in the body and can be recruited into damaged areas in the vascular phase. Studies have shown that damaged tissues recruit $Ly6C^{+}CCR2^{+}CX3CR1^{low}$ monocytes that transform into $Ly6C^{+}CX3CR1^{low}$ macrophages by means of specific markers, such as Ly6C and CX3CR1, in mice (Geissmann et al. 2003). These macrophages are short-lived and do not become $Ly6C^{-}CX3CR1^{high}$ macrophages (Geissmann et al. 2003). $Ly6C^{+}$ monocyte infiltration into muscle lesions is induced by chemoattraction from a CCL2-CCR2 axis during skeletal muscle regeneration (Arnold et al. 2007; Saclier et al. 2013; Varga et al. 2013). $Ly6C^{-}$ macrophages proliferate dramatically in the process of muscle regeneration. Recent data have shown that at the inflammatory stage (days 1–2), $Ly6C^{+}$ monocytes circulate into the muscle injury area within 24 h (Varga et al. 2016). During the transition stage (days 2–4), nearly all $Ly6C^{+}$ macrophages transform into $Ly6C^{-}$ cells, which then proliferate en masse (Varga et al. 2016). In the anti-inflammatory stage (days 4–8), $Ly6C^{-}$ macrophages activate the differentiation and fusion of myogenic cells into myofibers (Varga et al. 2016).

Macrophages are mainly divided into pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. After injury, the pro-inflammatory M1 macrophages are first recruited to the damaged area and secret cytokines, including IGF-1, IL-6, IL-1β, interferon-γ (IFNγ), and TNFα to stimulate the proliferation of myogenic precursor cells while inhibiting SC differentiation and fusion (Wosczyna and Rando 2018). Following this phase, anti-inflammatory M2 macrophages are present to support myogenesis and regeneration. M2 macrophages initially secret high levels of IGF-1 to induce ongoing SC proliferation, and then secret low levels of growth differentiation factor 3 (GDF3), TNFα, and TGFβ to promote myogenic differentiation (Juban and Chazaud 2017; Wosczyna and Rando 2018). In addition, TNFα secreted by macrophages induces FAP apoptosis,

whereas TGFβ secreted by macrophages has the opposite effect (Lemos et al. 2015). Finally, macrophages disappear when the myofibers are fully formed and return to homeostasis (Varga et al. 2016) (Fig. 1). These findings suggest that macrophages are not only crucial for efficient skeletal muscle regeneration, but also promote the coordination of many biological repair processes (Fig. 1).

Neutrophils

Neutrophils are derived from myeloid precursors in bone marrow. During inflammation, and injury, the number of neutrophils increases dramatically, and these cells eventually undergo apoptosis and are removed by macrophages and dendritic cells. Neutrophils kill pathogens by either an intracellular or extracellular pathway. Neutrophils phagocytose pathogens, and eliminate them through both NADPH oxygenase-dependent mechanisms (reactive oxygen species) and antibacterial protein-based (cathepsins, defensins, lactoferrin and lysozyme) mechanisms (intracellular pathway). Neutrophils can also release antibacterial proteins to exterminate microorganisms in the extracellular milieu (extracellular pathway). Highly activated neutrophils can also remove extracellular organic matter by releasing neutrophil extracellular traps (NETs), which are made up of core DNA elements and enzymes (Kolaczkowska and Kubes 2013). In the early stages of muscle injury, neutrophils circulate to the injured area, and release free radicals that target tissue fragments, which then engulf debris and degrade the muscle membrane in mice (Tidball and Villalta 2010). The number of neutrophils decreases swiftly after exerting specific biological effects (Fig. 1).

Eosinophils

Eosinophils are versatile lymphocytes that play a variety of biological roles in inflammatory processes, including parasitic helminth infections and allergic diseases. After stimulation, eosinophils are recruited and circulated into the inflammatory foci. Their receptors are bound to cytokines, immunoglobulins and complements, thereby modulating the immune response by releasing a series of pro-inflammatory cytokines, chemokines and lipid mediators (Rothenberg and Hogan 2006). Eosinophils are required for skeletal muscle regeneration. Muscle damage leads to the rapid recruitment of eosinophils, which secrete IL-4 to regulate the regenerative actions of the injured muscle (Heredia et al. 2013). IL-4 not only stimulates IL-4Rα$^+$ myoblast fusion and myofiber growth (Horsley et al. 2003), but also serves as a key factor of IL-4/IL-13 signaling, the activation of which promotes the proliferation of FAPs to support myogenesis while inhibiting their differentiation into adipocytes (Heredia et al. 2013) (Fig. 1).

T cells

T cells are a population of crucial adaptive cells that participate in cell-mediated immunity and normally exist in peripheral blood and secondary lymphoid organs, T lymphocytes are distinguished by their exclusive expression of CD4 and CD8 (Masopust and Schenkel 2013). Recent data have shown that the adoptive transfer of CD8 T cells into CD8α-deficient mice can promote muscle regeneration and block matrix remodeling (Spencer et al. 1997; Zhang et al. 2014). CD8$^+$ T cells can infiltrate into damaged muscles and facilitate the secretion of MCP-1 to recruit Gr1^{high} macrophages, which can foster the proliferation of myoblasts (Spencer et al. 1997; Zhang et al. 2014). In an injured muscle microenvironment, four pro-inflammatory cytokines, namely, IL-1α, IL-13, TNFα and IFN-γ, secreted by T cells are capable of promoting the proliferation of muscle SCs in vivo, and the continuous expansion of muscle SCs in vitro (Fu et al. 2015). In addition, heparin-binding vascular cell growth factors (HB-EGF), which are synthesized and secreted by CD4$^+$ and CD8$^+$ T cells, can improve wound healing (Blotnick et al. 1994). In comparison to CD4$^+$ and CD8$^+$ T cells, regulatory T cells (Tregs) occupy a large proportion of the lymphocytes accumulated in injured muscles, which is conducive to wound healing by coordinating with muscle stem cells (Sciorati et al. 2016). Tregs are distinguished by the expression of CD4, CD25, and FOXP3 (Fontenot et al. 2003, 2017), which are the vital transcription factors that mark Treg cell lineage (Josefowicz et al. 2012). Foxp3$^+$CD4$^+$ Tregs cells play an important role in the normal repair of skeletal muscles, and their homeostasis is regulated by IL-33. The prediminant IL-33-expressing cells exhibit a series of markers that can label FAPs, which are closely related to the nervous and immune systems and greatly affect the functions and traits of muscle (Kuswanto et al. 2016). It has been demonstrated that Tregs regulate the infiltration of myeloid populations into damaged tissues and control their numbers. Tregs facilitate their transition from a pro-inflammatory to an anti-inflammatory phenotype, which is instrumental for muscle regeneration (Leavy 2014). Tregs are also capable of regulating conventional T cell populations, particularly CD8$^+$ T cells (Burzyn et al. 2013). Additionally, muscle Tregs can secrete Amphiregulin, which is a growth factor that directly acts on muscle satellite cells in vitro and promotes muscle repair in vivo (Burzyn et al. 2013). These results suggest that T cells establish contact with immune cells or muscle progenitor cells and play a pleiotropic biological role in the process of muscle regeneration (Fig. 1).

Endothelial cells (ECs)

In response to injury, the number of ECs gradually increase and they generate several secretory factors including angiopoietin-1(Ang-1), IGF-1, hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF), which affect SC function in muscle regeneration (Tatsumi et al. 1998; Filigheddu et al. 2007; Hoeng et al. 2008; Mofarrahi et al. 2015) (Fig. 1). Recent studies have indicated that ECs can also secrete apelin and oncostatin M to enhance the frequency of SC proliferation and differentiation, as well as Periostin to promote SC differentiation (Latroche et al. 2017). These data demonstrate that ECs play an important role in regulating SCs, thereby affecting muscle regeneration (Fig. 1).

Fibroblasts

Fibroblasts play an important role in the differentiation of SCs. Studies have shown that fibroblasts make contributions to SC differentiation by promoting the fusion of co-cultured myoblasts (Mathew et al. 2011). Other studies have demonstrated that the reduction of $TCF4^+$ cells (considered to be mostly fibroblasts) weaken muscle regeneration (Murphy et al. 2011). These results suggest that fibroblasts have a far-reach meaning related to supporting muscle regeneration (Fig. 1). However, the biological effects and roles of fibroblasts in the process of muscle regeneration need to be further explored.

Pericytes

Pericytes are pluripotent cells that surround the blood vessels, and are beneficial for the repair and regeneration of various tissues upon injury. Pericytes are involved in several biological processes, including myogenesis, adipogenesis, fibrogenesis, neurogenesis and angiogenesis. There are two main subtypes of pericytes: type 1 (nestin-$GFP^-/NG2^+$) and type 2 (nestin- $GFP^+/NG2^+$) that express NG2, PDGFRβ, and CD146 in the skeletal muscle interstitium. Only type 2 pericytes contribute to myofiber formation in vivo (Birbrair et al. 2013a), but its reproducibility is affected by the regenerative milieu (Birbrair et al. 2013b). Pericytes induce muscle regeneration by interacting with SCs, and the biological factors released by apoptotic SCs can affect the regenerative capacity of pericytes. It has been shown that Alkaline Phosphatase (AP)-Cre^{ERT2}-labelled pericytes can fuse with growing muscle fibers and enter the muscle satellite cell chamber during postnatal development (Dellavalle et al. 2011). AP-lineage pericytes not only activate the myogenic program and fuse with existing myotubes, but have also been found to express the myogenic transcription factor MyoD in pathological tissues (Diaz-Manera et al. 2012). In summary, pericytes play an important role in skeletal muscle regeneration (Fig. 1).

Other cells

In addition to the above cells, there are a fraction of cells that exist in the skeletal muscle interstitium, which play an indispensable role in the process of muscle regeneration and are known as the collaborators of satellite cells (Tedesco et al.). Mesoangioblasts are cells isolated from the murine embryonic dorsal aorta that proliferate in vivo and are described as vascular-associated mesodermal stem/progenitor cells (De Angelis et al. 1999). Previous studies have shown that, in a microengineering model, human donor mesoangioblasts can restore dystrophin expression in DMD myotubes, more so than normal myoblasts (Serena et al. 2016). Mesoangioblasts are generally considered to be the active progeny of pericytes, thereby assisting in muscle regeneration.

PICs is a collective term for a population of cells that express the PW1/paternally expressed gene 3 (Cottle et al. 2017). They also express Pax7, but are located in the skeletal muscle interstitium and possess myogenic differentiation (Mitchell et al. 2010). PICs have been demonstrated to be different from the embryonic origin of satellite cells, showing a state of clonogenicity and multipotency in pig models, producing skeletal muscles, smooth muscles, endothelial cells, and adipocytes (Lewis et al. 2014).

AC133 cells are a subpopulation of human muscle-derived stem cells identified by Torrente et al. in 2014, which express the AC133 antigen and can differentiate into muscle cells, hematopoietic stem cells, and endothelial cells when stimulated by specific cytokines (Torrente et al. 2004). In mice, transplantation of hAC133 + cells can promote tissue perfusion, vascular growth and collateral expansion, reduce muscle necrosis and fibrosis, and ultimately promote muscle regeneration(Aranguren et al. 2011).

Conclusions

Skeletal muscle regeneration is a highly coordinated process in which several factors and multiple cell types are activated to remove the necrotic cellular debris and repair the damaged myofibers. The satellite and other functional cell types play important roles in muscle repair and regeneration. Several types of cells, including SCs, are directly involved in generating new myofibers, while other cell types secrete factors that regulate SC fate and regeneration. Therefore,

whether the injured skeletal muscle will fully regenerate is dependent on the resident progenitor cells, the infiltrating cells and the muscle extracellular matrix after injury. Although numerous studies have investigated the molecular regulation of SCs and muscle regeneration, the regeneration process is not yet completely understood. The function and regulation of cells involved in muscle regeneration have not been well-characterized. Furthermore, the interaction and crosstalk among the different cell types during the regenerative process have not been fully elucidated. Therefore, future studies are needed to obtain a more comprehensive understanding of the skeletal muscle regenerative process, as well as provide a basis for the development of better therapies for muscular disorders.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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