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Skeletal Muscle Fiber Types in Neuromuscular Diseases

Jennifer Glaser and Masatoshi Suzuki

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Abstract

In the human body, there are 600 individual skeletal muscles that allow us to perform a variety of functions such as executing locomotive tasks, breathing, and moving our eyes. The ratio of fiber types within the muscle critically contributes to determine the function of these muscles. Significant changes of muscle fiber types occur not only in normal development; changes have also been observed under abnormal conditions in neuromuscular disorders. In this review, we describe how muscle fiber types are specified during embryonic myogenesis, what potential factors are involved in the changes of fiber type composition, and how fiber type variations are influenced by the pathological conditions under specific neuromuscular disorders. Understanding skeletal muscle at the individual fiber level aids in studying the normal physiology and the pathology of disease in human.

Keywords: muscle fiber type, neuromuscular disease, skeletal muscle, Type I, Type II

1. Introduction

Skeletal muscle is the most abundant tissue in human body. Skeletal muscle accounts for approximately 20% of our resting energy expenditure [1], and composes 30–40% of one's body mass [2] depending on their fitness level [3]. As a part of the musculoskeletal system, skeletal muscle is connected to the skeleton to form part of the mechanical system that moves the limbs and other parts of the body. While skeletal muscle refers to multiple bundles of cells called muscle fibers, the composition of the individual fibers is different between muscle types. In this review, we describe how muscle fiber types are specified during embryonic myogenesis, what potential factors would be involved in the changes of fiber type composition, and how fiber type variations are influenced by specific disease conditions. Knowing the functional role of how muscle fibers contribute to and are affected by skeletal muscle diseases

aids in our understanding of the disease and provides insight to mechanisms of prevention, treatment, or cure of these conditions.

2. Skeletal muscle

Skeletal muscle plays important roles in the body that are concerned with movement, posture, and balance under voluntary control. Skeletal muscles are one of three major muscle types, the others being cardiac muscle and smooth muscle, and it is the most common of the three types of muscle in the body. As one component of the musculoskeletal system, skeletal muscle is attached to bones by tendons, and they produce all the movements of body parts in relation to each other. Unlike smooth muscle and cardiac muscle, skeletal muscle is under voluntary control. Similar to cardiac muscle, however, skeletal muscle is striated; it has long, thin, multinucleated fibers (known as myofibers).

3. Skeletal muscle development and fiber type specification

Skeletal muscle function seems to be maintained across mammals, but the composition of the individual fibers is different between muscle types [4]. Fiber type composition is initially defined in each muscle during embryonic myogenesis. In this section, we will go through the basic fundamentals of skeletal muscle development and fiber type specification (**Figure 1**).

3.1. Embryonic myogenesis

Studies investigating embryonic myogenesis have been extensively conducted in the embryos of zebrafish, chicken, and mice. After an embryo is generated, three germ layers (ectoderm, endoderm, and mesoderm) are formed. The mesoderm is characterized as paraxial, intermediate, and lateral mesoderm. The formation of skeletal muscle initiates from the paraxial mesoderm in early embryogenesis. In response to the signals from the notochord, neural tube, and surface ectoderm, the paraxial mesoderm forms segmented spheres termed somites. The somites are located as a pair on either side of the neural tube and the notochord and develop in a rostral-caudal direction. The somite is further specified as the dermomyotome, myotome, and sclerotome. The cells in the dermomyotome express the paired box transcription factors Pax3 and Pax7 [5, 6]. The cells in the dorsomedial and ventrolateral portions of the dermomyotome will give rise to the epaxial (primaxial) and hypaxial (abaxial) myotomes, respectively. Myf5-positive cells in the epaxial myotomes differentiate and form the trunk and back muscles. In contrast, MyoD-positive progenitors de-laminate and migrate from the hypaxial myotome into the developing limb as the source of limb muscles. MyoD and Myf5 are expressed in committed muscle cells, and are located in the myotome, which is form the maturation of dermomyotome lips [7–9]. The ventrolateral lip of the dermomyotome contributes to the hypaxial myotome, which is a source of precursor cells that form the trunk and thoracic vertebral column muscles. The dorsomedial lip of the dermomyotome contributes to the epaxial myotome, which is a source of muscles of the back. The process of myotome maturation originally initiates at the rostral part of the embryo and then extends to the tail [7].

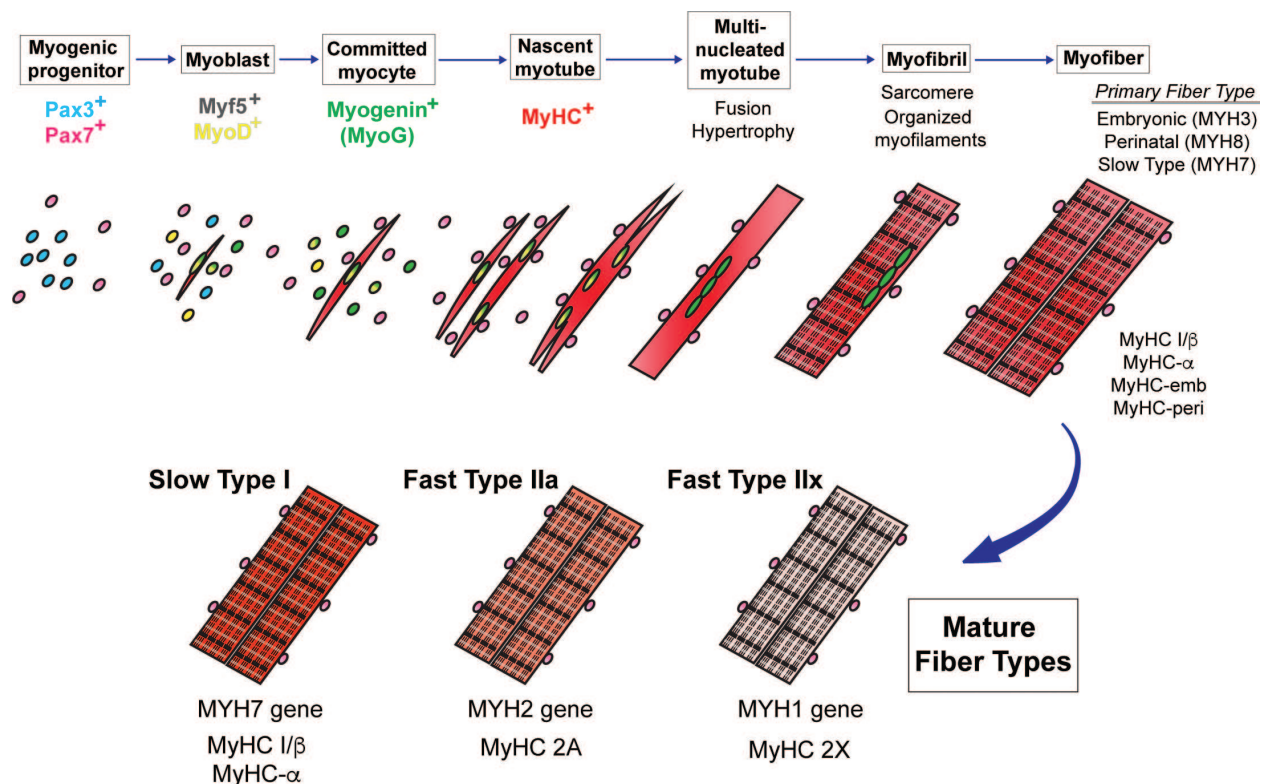


Figure 1. Skeletal muscle differentiation and fiber type specification. The terminal differentiation starts when Pax3⁺ and/or Pax7⁺ progenitors begin to express Myf5 or MyoD as committed myoblasts. These myoblasts gradually express myogenin (MyoG) and form single-nucleated nascent myotubes and multi-nucleated myotubes with myosin heavy chain (MyHC⁺). Actin, myosin, and elastic myofilaments are arranged to form organized sarcomeres within the myotubes. Primary myofibers express four isoforms of MyHC: MyHC I/β, MyHC-α, MyHC-emb and MyHC-peri. Development of fiber type continues as satellite cells differentiate and the fibers become innervated, forming mature fiber types. Different isoforms of myosin, MyHC I/β, MyHC-α, MyHC 2A, and MyHC 2x, are expressed. This figure is modified from Jiwwat et al. [10].

3.2. Terminal differentiation and myofiber formation

The terminal differentiation of progenitors and myoblasts initiates when myogenic progenitors in the dermomyotome stop dividing and exit the undifferentiated stage [10]. The progenitors differentiate into committed myoblasts, and form nascent myotubes following the maturation of the myotome [11]. More specifically, Pax3 and/or Pax7-positive proliferating progenitors are withdrawn from the cell cycle once the differentiation step is initiated (**Figure 1**). These progenitors become committed myoblasts expressing Myf5 and/or MyoD and then form the nascent myosin heavy chain-positive myotubes with myogenin-positive nuclei.

Two waves of myotube formation occur during skeletal muscle development, and sequentially give rise to primary and secondary myotubes [12]. Primary myotubes are generated from fusion of early myoblasts, and then align between muscle tendons. Late-stage myoblasts proliferate on the surface of primary myotubes and fuse to form secondary myotubes, and motor axons initiate innervation to the myotubes [12]. At this point, primary and secondary myotubes express specific isoforms of myosin heavy chain (MyHC), which can be used to broadly define two distinct fiber types, slow-twitch Type I and fast-twitch Type II myofibers.

Primary myotubes preferentially express Type I fibers [13, 14], while Type II fibers appear later during myogenesis [15, 16]. Single-nucleated myotubes then fuse with the nearby myotubes to form multi-nucleated myotubes. Thick-myosin and thin-actin filaments within the myotube begin organization and form a sarcomere structure, which is the functional unit of muscle contraction. Well-organized sarcomeric structure gives rise to a striation pattern in myotubes, representing many chains of myofibrils.

3.3. Fiber type specification

Primary myogenesis starts during the embryonic stage, when somatic stem cells express the genes Pax3 and Pax7 (**Figure 1**). This transforms the cells into myogenic progenitors, which migrate from the dermomyotome to form myocytes and primary myofibers. At this point of embryonic myogenesis, three isoforms of myosin heavy chain are expressed; slow MyHC (MYH7), MyHC-emb (MYH3), and MyHC-peri (MYH8) [17]. These primary myofibers serve as a template for the skeletal muscle to mature and differentiate. Secondary myogenesis progresses as satellite cells differentiate, become innervated, and mature myofibers are formed. In whole, genetic influences and motor neuron innervation during developmental differentiation determines the fiber types that one is born with [17]. Fiber type ratios determined at birth are not concrete throughout one's life however, as skeletal muscle chemical properties can change over time to meet physiological or pathological demands.

4. Muscle fiber types

Skeletal muscle tissue in humans is heterogeneous, composed of a variety of molecules [4]. The main functional proteins and structures within the muscle are maintained, such as mitochondria network, myosin, actin and titin. Yet, the specific isoforms of the molecules and the concentration of each monomer differ between skeletal muscles all throughout the body. These heterogeneous tissues are a resultant factor of evolution which allows each muscle to have a specialized function. The size of each whole muscle is determined by both the number and the diameter of muscle fibers that compose it. Individual muscle fibers are multi-nucleated, with each nucleus controlling the protein type, myosin that is translated in its surrounding. This is known as a nuclear domain [18].

Myosin is the main protein within skeletal muscle, and the certain isoform that is expressed determines the rate at which the muscle contracts, as well as its physiological properties. Within a single sarcomere of a skeletal muscle fiber, myosin heads and actin interact to form cross bridges. ATP hydrolyzation via ATPase is responsible for the energy to cause cycling of the myosin head and actin connections, which ultimately causes the muscle contraction. The type of myosin expressed is one factor that ultimately determines the fiber type. There are 11 total isoforms of myosin known to mammals [4, 19], which when expressed in different ratios compose a fiber type with distinct physiological properties. As discussed above, there are two categories of adult muscle fiber types in humans; Type I and Type II fibers (**Figure 1**).

Type I and Type II fibers are classified based on their myosin isoform, velocity of contraction and presence of physiological enzymes [3]. Type I fibers are also known as slow oxidative. Compared to Type II, they contain a higher number of oxidative enzymes and a lower number of glycolytic enzymes. They are rich in mitochondria and have a great capillary network to perfuse the fibers [20]. This contributes to their oxidative capacity. Type I muscle fibers predominantly contain myosin isoforms MyHC I/ β or MyHC- α , encoded by the gene MYH7 [17] and they contract slower and are more resistant to fatigue than Type II fibers. Because of their endurance properties, Type I fibers are commonly found in muscles mainly involved in posture, such as erector spinae, hamstrings, and gastrocnemius muscles.

Type II fibers on the other hand are fast to fatigue, as they have low oxidative capacity. These fiber types are recruited in short bursts of movement or power [3]. This is due to their greater maximal velocity of shortening, and abundance of glycolytic enzymes [3]. This in turn allows for quick energy utilization due to increased ATPase activity. There are two subcategories in human Type II fibers; Type IIa and Type IIx. Type IIa are classified as fast-oxidative glycolytic, a sort of combination between fast and slow contraction rates. Type IIx are fast glycolytic, having the fastest rate of contraction of all the human fiber types, yet the shortest time to fatigue. MyHC isoform genes MYH2 and MYH1 are expressed respectively in Type IIa and Type IIx fibers. The myosin protein isoforms present in each subtype are termed MyHC-2A and MyHC-2X [17].

Skeletal muscles are innervated by motor neurons which are responsible for the initiation of muscle contraction. Motor units are formed, consisting of a single alpha motor neuron that originates in the spinal cord that innervates a group of skeletal muscle fibers, all of the same fiber type. Changes in motor unit innervation of the skeletal muscle has shown to change the properties of fiber types innervated, therefore motor units too are contributors to the determinants of fiber type [21].

5. Factors influencing muscle fiber type composition

5.1. Physiological and pathological changes

Skeletal muscles have the property of plasticity. This means the composition of fiber types within a given skeletal muscle can change when under the influence of physiological changes such as mechanical stress and unloading. Further, abnormal health conditions caused by diseases and injuries also triggers significant changes of muscle fiber types [22]. The size and functional capacity of the muscle can be decreased upon injury, disease, or excess weight. As a result, scar tissue, connective tissue, or fat can take up mass that was once occupied by functional muscle [18]. When muscles become denervated, there is a tendency for slow to fast fiber transition [3]. This carries heavy implications for training status and disease state in humans [3, 23, 24].

5.2. Genetic and epigenetic controls

The physiological and pathological changes influence the levels of trophic factors, hormones, and nerve signaling associated with the muscle, which result in adaptive changes in muscle

fibers. The relative amounts of these factors and the extent of the changes that they can make are ultimately determined by genomic background and epigenetic control in individuals. The genes that one inherits controls and determines 40–50% of the ratio of Type I fibers within a muscle [3]. This means that physiological stressors can impact the plasticity of the muscles to a point, but in the end one's genetic make-up determines the extent to which the fiber types within the muscle can switch [3]. Like all cells in the body, the different fiber types contain the same genomic DNA sequence. MYH genes have been hypothesized to be clustered in a manner to facilitate temporal and spatial expression of these related genes [23]. Slow MyHC isoforms are located on chromosome 14, while chromosome 17 contains the fast and embryonic MYH genes in a cluster. The difference in gene expression, and resultant protein levels in a specific cell, are controlled by epigenetic mechanisms. As fiber types shift within a lifetime, the epigenetic profile within the cell is also affected, specifically in the amount of acetylation or deacetylation within the genome. This change is mostly seen within differentiating satellite cells, which are not fully mature [23]. Further, variations in expression levels of genes controlling systems such as mitochondrial biogenesis, glucose/lipid metabolism, cytoskeletal function, hypoxia, angiogenesis, and circulatory homeostasis would influence muscle fiber type. The frequency of alleles within a genome also impact the fiber type development [3]. Overall, there are many genetic factors at play such as single gene effects, gene–gene interactions and gene–environment interactions [3].

6. Muscle fiber types and musculoskeletal diseases

Neuromuscular diseases are caused by functional defects of skeletal muscles, directly via muscle pathology or indirectly via disruption of the nervous system. Most of these diseases are multi-faceted, and terminally result in wasting and atrophy of skeletal muscles. These abnormal conditions often lead to disabilities and complete loss of muscle function, with little to no cure. Pathology is best understood at the cellular level, and here we explore how the progression of the disease is involved in the changes of muscle fiber types, and how changes in fiber type may serve as a protective mechanism. Diseases covered in this chapter are mainly genetic in nature, having an uncontrollable disruption in cellular function that results in disease. This can either be inherited from previous ancestors or be sporadic in nature. This section will introduce several names of muscle and motor neuron diseases; however, this is not an exhaustive list.

6.1. Skeletal muscle diseases

6.1.1. *Sarcopenia*

Sarcopenia is a term that refers to the loss of lean body mass, particularly skeletal muscle, with an increase in aging [25]. This can be diagnosed through weakness within the body, difficulties walking, or dual-energy absorptiometry, which is a machine that tells the exact body composition of fat, bone mass and tissue. Sarcopenia at the individual fiber level is characterized by a loss of satellite cells associated with Type II fibers [18]. Organelles affected

in the myofibers include a decreased amount of mitochondria, an alteration in the sarcoplasmic reticulum, and hindered excitation-contraction coupling. Both Type I and II fibers have shown to be affected by losing their maximal force in both men and women. This is attributed to a loss of myosin expression within the cell, or oxidation of the myosin protein which inhibits the formation of crosslinks [18]. Surprisingly, the expression levels of myosin isoform MYH7, that of slow muscle fibers, are not affected [26].

6.1.2. Muscular dystrophies

Muscular dystrophies are a group of muscle diseases that result in the wasting of skeletal muscles, caused by muscle fiber necrosis [27]. The dystrophies involve mutations in genes that encode functional proteins involved in dystrophin or enzymes that modify the dystrophin proteins [18]. These mutations affect velocity of cross bridge cycling of actin filaments on myosin and of particular interest, they change the quality and force production of Type I and Type II fibers [18]. Apoptosis and necrosis in fiber types are a trademark of the disease, with caspase 3 being a known apoptotic gene that is upregulated in muscular dystrophies compared to unaffected individuals [27].

In Duchenne Muscular Dystrophy, Type II muscle fibers are the first to be affected with Type I muscle fibers following late in the disease progression [26]. Remaining Type I fibers are not similar to those found in healthy muscle. Degeneration and regeneration of diseased fibers is hypothesized to take place, due to coexpression of fetal MYH and slow MYH genes in adult muscle fibers [28]. Since Type II fibers are the most commonly affected in Duchenne Muscular Dystrophy, it is thought that inducing the expression of Type I fibers will alleviate both the symptoms and progression of Duchenne Muscular Dystrophy. A similar trend was found in another type of muscular dystrophy, Facioscapulohumeral Muscular Dystrophy, as there is an early decrease in Type II fibers and an overall increase in the number of Type I fibers [29]. On the contrary, in myotonic dystrophy, Type I fibers are affected, as they atrophy more frequently and they lose a greater amount of force generation compared to Type II fibers [30–32]. One hypothesis for this fiber type susceptibility to disease states is variation to transcriptional control of muscle fiber type. Genetic manipulations and pharmacological interventions have shown the effect of fiber type switching on disease states in mice [26]. For example, over expression of the transcriptional coactivator PPAR γ 1A rescues the cellular defects cause by the Dmd^{mdx} mutation via increased expression of Type I fiber contractile machinery and oxidative enzymes [26].

6.2. Motor neuron diseases

Motor neuron diseases are characterized by the progressive degeneration of motor neurons with subsequent functional loss. In the motor system, motor neuron axons carry the motor impulses from the spinal cord to the voluntary muscles. Innervation of alpha motor neurons from the central nervous system has a large part in determining the fiber type that is expressed within muscles. Motor units innervate muscle fibers in an “all or none” fashion, meaning a single motor unit innervates Type I and each subcategory of Type II fibers individually, and all the fibers that the motor unit innervate are of the same fiber type.

Co-expression of fiber types within a single muscle fiber has been seen in motor neuron diseases such as Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy [33]. In these diseases, specifically ALS, studying disease influence on skeletal muscles would provide valuable insight to the mechanisms of disease progression. Changes in muscle fiber types may occur at the early stage of diseases by reduced inputs from motor neurons, as disconnections between muscle and axon terminals have been observed in animal models of motor neuron diseases before symptom onset. Studying the disease onset in skeletal muscles has the potential to reveal the catastrophic pathology influence and the body's compensatory mechanisms to counteract disease progression [34].

Switches in muscle fiber type has been observed in patients in motor neuron diseases, however the switches cannot prevent the ultimate outcome: apoptosis and necrosis of individual muscle fibers [27]. Often, motor neuron diseases are diagnosed clinically via histochemical staining of muscle biopsies. Necrosis can be easily seen as fat or scar tissue under the microscope, but apoptosis is harder to identify due to the lack of inflammatory response from the body [27]. Denervation of the muscle results in upregulation of pro-apoptotic genes, such as bax and anti bcl-2, which are upregulated due to intrinsic cell stress. Muscle fiber atrophy is hypothesized to be caused by apoptosis induced degradation of a fiber's nuclei. This includes destruction of the nuclear lamina, the nuclear envelope, and DNA destruction [27].

6.2.1. Amyotrophic lateral sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal neurodegenerative disease caused by the selective loss of motor neurons in the spinal cord and brain stem. Motor neuron degeneration and neuromuscular junction denervation rapidly result in decreased motor function. Death typically results 3–5 years after diagnosis due to respiratory failure after loss of diaphragm control. About 90% of ALS cases occur sporadically; the remaining 10% are familial components. Approximately 70–80% of familial ALS have mutations of the $\text{Cn}^{2+}/\text{Zn}^{2+}$ superoxide dismutase 1 (*SOD1*), *TDP43*, *FUS*, or *C90ORF72* genes [35].

Although a disease cause of sporadic ALS has not been specified, this disease is generally regarded as resulting from factors involving environment, lifestyle, aging, and genetic predisposition [36]. Several proposed pathological mechanisms of disease include protein misfolding and aggregation, glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, glial cell activation and related inflammatory processes, and axonal transport defects [37].

ALS causes motor neuron death and gradual denervation of skeletal muscles over time. This denervation causes loss of muscle function and muscular atrophy within affected cells, ultimately resulting in cellular death due to apoptosis. While many of existing ALS therapies are expected to promote motor neuron survival in the spinal cord or motor cortex [38], looking at the pathologies within skeletal muscle gives support for the “dying-back” hypothesis. This hypothesis states that irregularities within the skeletal muscle are the primary cause of ALS, denervating muscle and motor neuron [39]. Based on this hypothesis, possible contributions of skeletal muscles and neuromuscular junctions in ALS pathology have been proposed in recent studies. Specifically, our research group also reported that using stem cells to deliver growth factors directly into the skeletal muscle could restore motor function in a rat model of

familial ALS [40–42]. Our approach can sufficiently protect motor neurons by preventing the “dying back” of these cells from the skeletal muscle in ALS.

While the majority of ALS patients have limb onset, about 25% of cases eventually diagnosed with ALS have bulbar onset which strikes the corticobulbar area in the brain stem. This section controls muscles in the face, neck and head. Bulbar onset usually affects voice and swallowing first. Patients with bulbar onset have a correlation between the age of death and the loss of slow tonic fibers, although there is neither correlation seen in spinal onset ALS nor controls [34].

ALS pathology affects skeletal muscle in many ways, which seems to influence muscle fiber type changes. Autopsies show fiber atrophy, fiber grouping, fiber splitting, with increased fatty tissue and connective tissue [43]. Interestingly, unlike atrophy from exercise, ALS shows a fast to slow fiber type switch [39, 44]. In the hindlimb muscle (tibialis anterior muscle) of pre-symptomatic ALS model mice, there is denervation of the most forceful and fast to fatigue fibers Type IIB (only found in mice). This results in transitions to fast motor units with intermediate fatigue and fatigue resistant fibers. Although this transition is present, it is not a sudden change nor a complete loss of Type IIB fibers [44]. Biopsies taken from atrophied skeletal muscles in patients with ALS have shown that individual muscle fibers contain myosin isoforms corresponding to both fiber Types I and II, termed a mixed fiber type. An early pattern of denervation can be detected and has the potential to be used for diagnostic purposes. This pattern is individual fibers with a mixed fiber type and little fiber type grouping, all within an atrophying muscle [45].

It has been reported that specific muscle groups such as extraocular muscles are relatively spared from the disease phenotype in ALS [46]. Motility of the eye is often maintained in ALS patients [47] and autopsies have shown the extraocular muscles do have some muscle fiber pathology compared to control, but in relation to other ALS affected skeletal muscles in the body, the extraocular muscles were well preserved [43]. The pathology that was seen include change in fiber type composition, the cellular architecture, and decreased overall MyHC content. Embryonic MyHC was almost nonexistent in the extraocular muscles in those affected by ALS [43].

This preservation of extraocular skeletal muscle is accredited to the distinct fiber type composition within the extraocular muscles. Extraocular muscles have a unique myosin expression that is not found in skeletal muscles located other places of the body. Along with Type I and Type II fibers, a special myosin isoform, MyHC extraocular, is present and Type I fibers seem to express two separate forms of MyHC, of specific interest MyHC α cardiac. [43]. Embryonic MyHC has notable expression in the extraocular muscles, as healthy human controls show co-expression of embryonic MyHC in Type II fibers, while ALS patients had no embryonic MyHC expression [43, 48].

Although there is great speculation, the exact mechanism of why extraocular muscles are spared in ALS is unknown. However, one interesting hypothesis is the multiple innervations of slow tonic fibers serve as a protective mechanism against the neurodegenerative disease [48]. It has also been found that the motor neurons of the extraocular muscles have different surface markers than motor neurons found elsewhere in the body, suggesting they have

properties that make the neurons less susceptible to disease [49]. As an additional note, similar specific insusceptibility in the extraocular muscles has also been observed in Duchenne Muscular Dystrophy [50].

Another question is how sex influences fiber type specification in the muscle during ALS pathology. The exact etiology of ALS is still uncertain, but most epidemiological studies have shown a higher incidence of ALS in men than women. Interestingly, sexual dimorphism in disease onset and progression is also observed in rodent models of familial ALS [51, 52]. Although it is still uncertain whether such sexual differences are originated from the intrinsic difference in individual cells [53], further studies would be required to answer this question.

6.2.2. *Spinal muscular atrophy*

Spinal Muscular Atrophy (SMA) is a group of motor neuron diseases, which are autosomal recessive in nature. Each SMA type has a different clinical outcome, however all SMA types commonly demonstrate motor neuron degeneration caused by insufficient expression of a specific protein named Survival of motor neuron (SMN) [54]. The clinical severity of SMA ranges from I–IV, with IV being the least severe. I is infantile SMA that causes death early in childhood and IV involves some motor neuron loss, but allows for a normal life expectancy [55].

All cases of SMA result from reductions in levels of the SMN protein. Specifically, SMA is caused by deletion or mutation of the survival motor neuron gene (SMN1). The SMA disease is present in a spectrum of disease severities ranging from infant mortality, in the most severe cases, to minor motor impairment, in the mildest cases. The variability of disease severity inversely correlates with the copy number, and thus expression of a second, partially functional survival motor neuron gene, SMN2.

In type III SMA-induced mice, muscle atrophy resulted in a transition to slower, oxidative phenotype. This meaning that there were more Type I fibers in the soleus muscle and Type II fibers in fast twitch muscles transitioned to a more oxidative fiber type [54]. These same mice also had smaller motor neurons units than controls and the Type I motor neurons decreased in size as the disease progressed. Other studies that have used type III SMA-induced mice have shown to have increased fiber type grouping compared to wild type [56].

There has been evidence that these pathological changes in muscle fiber types can be reversed. Swimming aided the mice to regain more glycolytic fast twitch fibers, and restore Type I motor unit size close to wild type levels [54]. Running produced more Type I fibers compared to sedentary SMA mouse control [54] and was able to restore SMA fast fiber types. Upon completion of exercise intervention by type III SMA-induced mice, their structure and number of the Type I fibers were comparable to controls [54].

In humans, it has been shown that innervation of fibers in children with SMA (specifically Werdnig-Hoffmann disease) is incomplete. This results in atrophy of fibers and the inability of fetal MyHC to switch to adult Type I and Type II myosin. When this observation was tracked through childhood it showed that in infancy, there is a large increase in the number of Type I fibers, and no detectable Type II fibers by 20 months. This further emphasizes the need for motor neuron innervation for Type II fibers to prevail [4, 57].

7. Conclusions

Muscle fiber type composition is primarily determined during development but will be altered by physiological and pathological conditions. Significant changes of fiber type composition have been identified in the muscles with a background of major neuromuscular diseases. To further understand the roles of muscle fiber composition in skeletal muscle development and diseases, additional studies using new research approaches may help us understand how muscle fiber type specification occurs during development and disease conditions. For instance, skeletal muscle cell culture derived from human pluripotent cell resources can provide a new tool to study how human skeletal myocytes differentiate into myotubes with specific fiber types in culture [58, 59]. These studies could highlight what specific mechanisms are involved in the significant changes of fiber type composition and ratio in the skeletal muscle during embryonic myogenesis and under disease conditions, and how these changes of muscle fiber types impact on muscle physiology and pathology.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Author details

Jennifer Glaser and Masatoshi Suzuki*

*Address all correspondence to: masatoshi.suzuki@wisc.edu

Department of Comparative Biosciences, University of Wisconsin Madison, Madison, Wisconsin, United States of America

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