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MUSCLE INJURIES (SJ MCNEILL INGHAM, SECTION EDITOR)

Normal muscle structure, growth, development, and regeneration

Wladimir Bocca Vieira de Rezende Pinto[1] · **Paulo Victor Sgobbi de Souza**[1] · **Acary Souza Bulle Oliveira**[1]

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Abstract Knowledge about biochemical, structural and physiological aspects, and properties regarding the skeletal muscle has been widely obtained in the last decades. Muscle disorders, mainly represented in neuromuscular clinical practice by acquired and hereditary myopathies, are well-recognized and frequently diagnosed in practice. Most clinical complaints and biochemical characterizations of each myopathy depends on the appropriate knowledge and interpretation of pathological findings and their comparison with normal muscle findings. Great improvement has been obtained in the last decades mainly involving the mechanisms of normal muscle architecture and physiological function in the healthy individuals. Genetic mechanisms have also been widely studied. We provide an extensive literature review involving current knowledge regarding muscle cell structure and function and embryological and regenerative processes linked to muscle lesion. An updated comprehensive description involving the main nuclear genomic regulatory mechanisms of muscle regeneration and embryogenesis is provided in this review.

Keywords Muscle · Physiology · Regeneration · Development · Satellite cell

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✉ Wladimir Bocca Vieira de Rezende Pinto
wladimirbvrpinto@gmail.com

Paulo Victor Sgobbi de Souza
pvsgobbi@gmail.com

Acary Souza Bulle Oliveira
acary@neuro.epm.br

[1] Division of Neuromuscular Diseases, Department of Neurology and Neurosurgery, Federal University of São Paulo (UNIFESP), Estado de Israel Street, 899. Vila Clementino, São Paulo, SP 04022-002, Brazil

Introduction

Neuromuscular diseases represent an important group of neurological disorders in clinical practice, often taking part as differential diagnosis of systemic conditions with secondary neurological compromise or with primary motor unit disorders, including diseases of the lower motor neuron and its axon, neuromuscular junction or the skeletal muscle, or peripheral sensory pathways, including the axon of sensory nerve and sensory ganglia of the spinal nerve. Myopathies represent the acquired or genetic muscle diseases that manifest themselves in a wide clinical spectrum, depending on the age of symptomatic onset, genetic and molecular basis, and the type of structural dysfunction associated in the myofiber. Myopathies may present as isolated or exercise-induced myalgia, isolated muscle stiffness or sometimes triggered by specific factors (environmental and drugs), diffuse or localized myalgia, muscle weakness (usually global or proximal in the limbs, eventually distal), muscle fatigue, dysphagia, diplopia (with extraocular muscle involvement), isolated or recurrent myoglobinuria, muscle atrophy, muscular pseudo-hypertrophy, and dysfunction related to extra-skeletal muscles (including cardiomyopathies) [1, 2].

The number of primary muscle diseases secondary to different structural or metabolic genetic mechanisms has increased recently and brought many difficulties related to clinical diagnosis, immunohistochemical analysis, and genetic and molecular testing in some situations. More than 40 different loci are associated with the different genetic and clinical presentations of myopathies (Table 1) [1, 9]. So, many of the previous ideas regarding structural and architectural aspects of the normal muscle, its intracellular metabolic pathways, and their interaction with the microenvironment of the extracellular matrix underwent extensive update in the last decade, especially in topics related to molecular pathways which control

Table 1 Current classification of muscle disorders and genes involved, according to the gene table of monogenic muscle diseases from World Muscle Society [1, 3–8]

Classification of muscle disorders (World Muscle Society, 2014)	
1) Muscular dystrophies	Duchenne/Becker muscular dystrophy (*DMD*), Emery-Dreifuss (*EMD, FHL1, LMNA, SYNE1, SYNE2, TMEM43*), Limb-girdle muscular dystrophy (*MYOT, LMNA, CAV3, DNAJB6, DES, TNPO3, HNRPDL, CAPN3, DYSF, SGCG, SGCA, SGCB, SGCD, TCAP, TRIM32, FKRP, TTN, POMT1, ANO5, FKTN, POMT2, POMGNT1, PLEC1, DES, TRAPPC1, GMPPB, DAG1, ISPD*), facioscapulohumeral muscular dystrophy (*DUX4, SMCHD1*), other muscular dystrophies (*TOR1AIP1, VCP, DPM3, PTRF*)
2) Congenital muscular dystrophies (CMD)	Merosin-negative CMD (*LAMA2*), rigid spine CMD (*SEPN1, FHL1, ACTA1*), muscle eye brain disease (*POMGNT1, FKRP, POMT2, GMPPB*), Fukuyama CMD (*FKTN*), Walker-Warburg syndrome (*FKTN, POMT1, POMT2, PKRP, B3GNT1, GTDC2, ISPD, POMGNT1*), integrin-related CMD (*ITGA7*), myosclerosis (*COL6A2*), DNM2-related CMD (*DNM2*), Ullrich type CMD (*COL6A1, COL6A2, COL6A3*), Bethlem myopathy (*COL6A1, COL6A2, COL6A3*), TCAP-related CMD (*TCAP*), LMNA-related CMD (*LMNA*), other phenotypes with hypoglycosylation (*FKRP, LARGE, DPM1, DPM2, ALG13, B3GALNT2, GMPPB, TMEM5, POMK*), other CMD (*CHKB* megaconial)
3) Congenital myopathies	Nemaline myopathy (*TPM3, NEB, ACTA1, TPM2, TNNT1, KBTBD13, CFL2, KLHL40, KLHL41*), Congenital fiber type disproportion myopathy (*ACTA1, SEPN1, TPM3, RYR1, MYH7*), myotubular myopathy (*MTM1*), centronuclear myopathy (*DNM2, BIN1, RYR1, TTN, SPEG*), multiminicore disease (*RYR1, SEPN1, MEGF10*), Central core (*RYR1*), cap disease myopathy (*TPM2, TPM3, ACTA1*), other myopathies (*MYHA, TRIM32, CNTN1, MYH2, TTN, MYBPC3, RYR1*)
4) Distal myopathies	*DYSF, TTN, GNE, MYH7, MATR3, TIA1, MYOT, NEB, CAV3, LDB3, ANO5, KLHL9, DNH2, FLNC, VCP*
5) Other myopathies	Myofibrillar myopathy (*CRYAB, DES, SEPN1, LDB3, MYOT, FLNC, BAG3*), miscellaneous (*LAMP2, VMA21, PABPN1, TTN, PLEC1, GDF8, ACVR1, CAV3, FHL1, VCP, ICSV, RYR1*)
6) Myotonic syndromes	Myotonic dystrophy types 1 (*DMPK*) and 2 (*ZNF9*), other types (*CAV3*, *HSPG2*, *ATP2A1/SERCA1*)
7) Ion channel muscle diseases	Chloride channel (*CLCN1*), sodium channel (*SCN4A*), calcium (*CACNA1A*), potassium (*KCNE3, KCNA1, KCNJ18*)
8) Malignant hyperthermia	*RYR1*, *CACNA1A*
9) Metabolic myopathies	Glycogenosis (*GAA, AGL, GBE1, PYGM, PFKM, PHKA1, PGM1, GYG1, GYS1, PRKAG2, RBCK1*), glycolytic pathway disorders (*PGK1, PGAM2, LDHA, ENO3*), disorders of skeletal muscle lipid metabolism (*CPT2, SLC22A5, SLC25A20, ETFA, ETFB, ETFDH, ACADVL, ABHD5, PNPLA2, ETFDH, LPIN1*)
10–16cy Other groups of neuromuscular diseases	Hereditary cardiomyopathies, congenital myasthenic syndromes, motor neuron disease, hereditary ataxias, hereditary motor and sensory neuropathies, hereditary paraplegias; other neuromuscular disorders

myogenesis in adult and embryonic periods and basic functions and regulatory roles of satellite cells. The objective of this review is to present the most current aspects regarding embryonic and postnatal muscle development mechanisms, the molecular structure of the contractile apparatus and the normal cytoarchitecture, and regenerative and plasticity mechanisms of the muscle in atrophy and hypertrophy.

Structure and functions of the normal muscle

The striated skeletal muscle relates to regular, fast and powerful muscle contractions and discontinuous voluntary action, differentiating the same from smooth and cardiac muscle. Regarding its structural organization, normal skeletal muscle has elongated muscle fibers with large diameter and uniform shape with multiple peripheral elliptical cell nuclei in subsarcollemmal position and homogeneous cytoplasm, rich in myofibrils and surrounded by connective tissue in the endomysium. The set of muscle fibers is organized in fascicles surrounded by thin connective tissue perimysium and the global muscle bulk (i.e., gastrocnemius, deltoid and biceps brachialis muscles) is also surrounded by collagen-filled connective tissue epimysium. The arterial blood supply comes from different branches related to each muscle group, and each type I muscle fiber, as will be discussed later, has more energy demand than the others [1, 3].

As previously described, the proper function of muscle contraction depends on the normal function and integrity of all motor units in all its components. Each motor unit accounts on average to the innervation of 100 to 10,000 muscle fibers, depending on the main physiological role of the muscle bulk. Further than determining each histochemical muscle fiber type, the motor unit stimuli participate through direct trophic factors and chemical stimuli of the post-junctional membrane in the motor plate [3]. Knowledge regarding all membrane elements of the post-junctional membrane has grown a lot in the last decades, overcoming the simple model of acetylcholine receptor (AchR) role and cholinergic neuromuscular transmission, and disclosing the previously unknown functions of the complex glycoprotein system including rapsyn (and its associated transmembrane linker/RATL), utrophin, syntrophins, agrin, dolichol kinase-7 (DOK-7) and muscle-specific kinase (MuSK), and also the epidermal growth factor (ErbB) receptor, biglycans, and SCN4A sodium voltage-gated

channel. Each different component plays specific roles during neurochemical and electrical stimuli in the motor plate. There is also important coupling of this membrane complex to the dihydropyridine receptor (DHPR) system in the T-tubule of the striated skeletal muscle, activating the intracellular sarcoplasmatic membrane system of the ryanodine receptor (RYR1) and also modulating indirectly other membrane receptors involved in the sarcoplasmic reticulum uptake of calcium, including junctin, triadin, and SERCA (sarco/endoplasmic reticulum calcium-ATPase) [2, 3]. As a consequence, there is intracellular release of calcium from the intrasarcoplasmic compartment to the cytoplasm, thus allowing the proper muscle contraction initiation by the actomyosin complex [3, 10].

The myofibrillar protein portion represents up to 85 % of muscle fiber volume [11]. The sarcome contractile filaments organize in thick filaments (including the actin-binding of ATP to the myosin head site) and thin filaments (composed by G-actin and troponin complex. Z-disk or line relates to muscle fiber adaptation to mechanical stress and includes different protein types, such as calcineurin, actin, α-actinin, nebulin, γ-filamin, myotilin, titin, ZASP (Z-band alternatively spliced PDZ motif protein), myogenin and telethonin. M-line is represented by myosin thick filament. Major sarcomeric function involves the myosin head ATPase activity which enables the flexion of the myosin head in the thick filament to move the thin actin to short the I-band [10].

Shortly, it is essential to describe the coupling phenomenon between the actin and myosin filaments in actomyosin complex through the cross-bridges during muscle contraction. There are different phases of cyclic coupling: rest, excitation, contraction, restoration, and relaxation. In the resting phase, there is no interaction of the filaments, keeping the ATP molecule attached in the cross-bridge terminal and the calcium ion into the sarcoplasmic reticulum. In the excitation and activating phase, the nerve impulse reaches the myoneural junction, releasing calcium from the sarcoplasmic reticulum and saturating troponin and modifying the conformational structure of troponin, exposing the binding site and releasing the site for actomyosin complex formation with ATP molecule in the myosin complex. In the contraction phase, there is activation of myosin ATPase by the actomyosin complex, providing ATP breakage and promoting energy release, while myosin binds to on actin and makes it slips (the so-called ATP-dependent muscle contraction). In the restoration phase, ATP enters the complex, inactivating the actomyosin complex [10, 12]. In the late relaxation phase, there is calcium uptake by the sarcoplasmic reticulum again and muscle relaxation starts until the next rest period and then a new cycle starts. Until the next excitation phase, there will be the need for a new electric stimulus to provide new coupling, requiring again the normal function of ion voltage gated-dependent channels in the postsynaptic membrane [3, 12, 13].

Despite the complex steps involved in coupling and muscle contraction, other protein components associates to the plasma membrane, the endoplasmic reticulum (including N-seleprotein, protein-O-mannosyltransferases POMT1/POMT2), the intermediate filament, the costamere, and the extracellular matrix. During sarcomere structure maintenance, nebulin regulates normal length of the thin filaments of actin and titin couples the thick filament of myosin from the M-line to the Z-disk and maintenance of the passive sarcomere tension. Desmin is also a component of the intermediate filament responsible for the union of the myofibriles from the Z-disk, muscle membrane, and muscle fiber nucleus. Costamere represents the protein complex linking the sarcolemma, cytoskeleton, and extracellular matrix, including major components frequently disrupted in different inherited myopathies (dystroglycans, sarcoglycans, sarcospan, Grb2, α-dystrobrevin, and syntrophins) all involved at some point in F-actin binding in the intracellular compartment by dystrophin and in basal membrane in extracellular matrix binding by agrin, perlecan, neurexin, and laminin-α2 [9, 14, 15]. Another important system links α- and β-integrin to laminin-α2 in a costamere-independent complex [14]. Golgi complex-associated proteins are also linked to different functions and disorders, including fukutin-related protein (FKRP), fukutin, protein O-linked mannose-*N*-acetylglucosaminyltransferase 1 (POMGnT1), and LARGE (acetylglucosaminyltransferase-like 1A) [2, 9]. The main genes involved in coding all this muscle components and frequently involved in inherited myopathies are described in Table 1 [1, 9, 16].

Genetic and molecular mechanisms of muscular embryogenesis

The role of muscle embryogenesis in the comprehension of some osteomuscular congenital dysfunctions is critical, as it will be further described. Muscle embryogenesis starts during bilateral somite formation in the paraxial mesoderm near the neural tube, neural crest and notochord under their paracrine signaling. The main determining factors of myoblast differentiation in summary are MyoD, Mrf4, Mef2, Myf5, and myogenin [17]. However, a complex process of molecular inhibition and activation during developmental stages takes part.

The origin of the striated skeletal muscle is based from the muscle progenitor cells from the hypaxial of the somite and dorsal portion of the mesoderm (the so-called dermomyotome). These muscle progenitor cells from the hypaxial portion of the dermomyotome delaminate (depending on Pax3/7, cyclin-D1, Myf5, and MyoD expression) and migrate to the limb bud (by HGF, FGF and Sonic hedgehog release by the mesodermal tissue, and Wnt/β-catenin pathway stimulus), proliferating and expressing myogenic determining factors in the limb (giving rise to ventral and dorsal muscle masses by expression of

MyoD and Myf5 and Msx1 in the distal muscles). Myoblasts originate from differentiation and then differentiate to adult striated myotubes and myocytes. Other molecular mechanisms also play important roles during late muscle development: (i) MRF4 and MLP also participate in the innervation process and induce late maturation of myotubes; (ii) myofiber fusion and differentiation depends on different molecule expression (Eya2, Six1, Myf5, MyoG and Mrf4); (iii) Mox2, Lbx1 and c-met participate in the late phase of specific muscle patterning, according to a dorsal to ventral polarization. There is also a high contribution of molecular mechanisms involving Wnt7α release by the zone of polaring activity in the limb bud and the stimulation of Sonic hedgehog (Shh) pathways by the dorsal ectodermal tissue. It is also important to highlight the outstanding role of the epaxial dermomyotome involved in deep paravertebral muscle development under the expression and upregulation of Lbx1 [18–20]. It has also become more widely known the role of type 2 perivascular pericytes during the muscular regeneration and primary myogenesis [21].

Genetic and molecular mechanisms involved with muscular atrophy and hypertrophy

Muscle plasticity concept also includes the complex molecular mechanisms of atrophy and hypertrophy. Skeletal muscle represents a highly plastic tissue. From a simple point of view, skeletal muscle growth or hypertrophy and muscle wasting or atrophy result both from complex changes in intracellular signaling pathways in the nucleus and cytoplasm, involving the components of the Akt/mTor and the p38 MAPK pathways. MK2 (mitogen-activated protein kinase-activated protein kinase 2) participates in the regulation of muscle mass and determines the subcellular localization of p38 in muscle fibers, being phosphorylated and both exported from the nucleus in a complex with p38, involved with skeletal muscle growth [22].

Muscle hypertrophy represents an intracellular process secondary to anabolic exercise stimuli through the block of proteolytic pathways, activation of actin and myosin protein synthesis and activation of satellite-cells. Muscle hypertrophy must be differentiated from hyperplasia and can be divided in two main types: (i) myofibrillar, in which an increase in contractile sarcolemmal components occurs, mainly represented by actin and other thick filamento components; and (ii) sarcoplasmic, in which there is an increase in noncontractile components, mainly represented by sarcoplasmic reticulum, glycogen, and creatine-phosphate [23, 24]. Anabolic pathways are mainly represented by activated Akt-IGF-1 pathways with increased protein synthesis by mTOR pathway activation and GSK-3β inhibition. There is also an IGF-1-mediated muscle mass growth depending on mTOR linked to TSC2 and Akt, leading to activation of p70S6K and other nuclear transcription factors, including PHAS-1, leading to muscle hypertrophy. It has also been demonstrated downregulation mechanisms of some components of ubiquitin-proteasome system by FOXO (Forkhead box O family) phosphorylated action, which is inhibited by Akt indirectly by nuclear action of atrogin-1, which inhibits muscle atrophy [11]. Mef2 and MyoD also take their roles in STARS (striated muscle activator of Rho signaling) pathway activation changing G-actin, myocardin-related transcription factors, and SRF (serum response factor), leading to muscle growth [19].

Muscle atrophy results from multiple different physical, biochemical, and electrical stimuli. The main molecular mechanism is lack of Akt activation by different mechanisms (chronic denervation, immobility, and drug-induced stimuli), promoting then FOXO phosphorylation (modulating atrogin-1 and MuRF1) and enhancing degradation of troponin I, titin, MHC-II, and myosin by the ubiquitin-proteasome pathway and, thus, leading to atrophy. Cachexia states in chronic inflammatory systemic disorders and malignancies promote the release of TNF-α and IFN-γ leading to NFκB translocation to the nucleus through IκB/TAK-1 pathways and decrease in MyoD, indirectly leading to MuRF1 and atrogin-1 increases and, thus, leading to atrophy. A decrease in muscle tension forces also dissociates titin from MuRF, giving rise to ubiquitination of nuclear proteins and thus changing NFκB pathway leading to muscle atrophy. Phosphoinositide 3-kinase (PI-3K), as an additional pathophysiological mechanism, activates the Akt pathway and the caspase-3, promoting nuclear apoptosis through Bax and fragmenting actin thin filamento and its degradation through the classical ubiquitin-proteasome system [19]. Another widely studied mechanism of muscle atrophy involves de direct action of IGF-1 (insulin-like growth factor-1) phosphorylation IRS1 receptor leading to ubiquitin and Akt/mTOR pathways activation. Myostatin is a member of the TGF-β family, an inhibitor of muscle growth by Smad2/3 pathway leading to secondary muscle atrophy [1], in a similar way as ativin IIB and IB by p38/MAPK pathway and ACTRII, leading to PI-3K inhibition. Additionally, HDAC4, previously described, activates myogenin leading to MuRF1 stimulation and muscle atrophy [25]. There is also a widely proven association of KELCH protein family as intracellular regulators of E3-ubiquitin ligase system in the control of protein turnover [26].

Molecular mechanisms involved to satellite-cell activation and role

Muscle regeneration is the muscle response to variable muscle injury causing inflammatory responses and satellite cell activation. The satellite cells are self-renewing quiescent muscle progenitor cells located between the basement membrane and mature muscle fibers, which become readily activated by many different stimuli and mechanisms, proliferate and differentiate. This step represents the initial, major, and transient event during striated muscle regeneration. These cells remain

quiescent in adults, but with a high capacity and sensibility to re-enter the cell cycle and to express p38-phosphorylated and MyoD and high levels of Cdc6 (cell division cycle 6) and other cyclins and its kinases. Nitric oxide stimulation activates satellite cells causing the release of HGF (hepatocyte growth factor) to the extracellular matrix, leading to activation of c-met receptors, proliferation, and inhibiting differentiation of these satellite cells. The same mechanisms of activation have described previously in relation to other stimuli (mechano-growth factor, MAPK, TGF and FGF2/8, syndecans, matrix metalloproteinases-2/9 and collagen VI). Another common pathway is the stimulation of the Notch pathway with satellite cell proliferation and the Wnt/β-catenin pathway leading to differentiation in to myoblasts. Activated satellite cells leave their typical location after activation, proliferates and begin to express MyoD, Pax3/7 and Myf5, mimicking at some point the general molecular expression seen during the embryonic period. Myoblasts fuse and form myotubes, which then fuse with mature muscle cells in the injured myocytes, and then expressing myogenin. The final step of myotube maturation occurs leading to enhanced production and expression of specific muscle proteins in immature forms and expression of MRF4 and enhanced production of myogenin. The main regenerative pathways activated after muscle injury in satellite cells, in short, involve NOTCH1/3, Wnt/β-catenin, TGF-β, and IL-6 pathways. Although nearly obvious, recently, it became more clear that most of clinical signs related to an acquired or inherited myopathy correlate to the degree of loss of satellite cells [27–30]. Age-related sarcopenia also correlates with a lesser expression degree of Pax7, IGF-1, and higher levels of Sprouty1 factor, PPARs (peroxisome proliferator-activated receptors), and PGC1α (PPARS gamma coactivator 1-α) [31, 32]. As microRNAs (miRNAs) molecular biology became more widely known, muscle-specific miR-206 began to take a major role during muscle differentiation by Pax3/7, its inhibition by TGF-β and its inhibitory effect in DNA polymerases and histone deacetylase systems [33]. These new molecular pathways represent the major contribution and perspective for therapeutic development in progenitor muscle cells and satellite cells.

Genetic and molecular mechanisms involved in muscle plasticity between histochemical fiber type

All muscle fibers innervated by a given type of motor unit are of the same histochemical type and stands generally near one to the other, but not grouped with each other, giving the typical appearance of "mosaic" between different histochemical fibers in different techniques (myofibrillar myosin ATPase pH 4.6 and pH 9.4, NADH-TR, cytochrome oxidase, succinate dehydrogenase, phosphofructokinase) [3]. Two main types of muscle fibers have been delineated. Type 1 (or slow twitch) fibers are very oxidative and present with slow contraction, being recruited during long-duration physical activities or high resistance, by its greater response to endurance exercises and fatigue resistance. Type 2A presents with a fast twitch pattern with oxidative and glycolytic activities, being mostly recruited during short and high intensity activities, and presenting with high levels of phosphofructokinase and succinate dehydrogenase. Type 2B presents with a higher glycolytic and anaerobic capacity and thus more fatigable contractions during tasks. Each muscle presents with a specific proportion of different fiber types [3].

Muscle plasticity represents one of the most recent topics in molecular neuromuscular studies and allowed the comprehension of exchanges from type 1 to type 2 fibers and vice versa trough different acute or chronic stimuli, including chronic diseases, several myopathies, electrical stimulation, and physical exercise. Reinnervated muscle fibers after a post-denervation state assume metabolic and mechanical properties of the new motor unit from the distal portions of the surviving axons coming by side. This mechanisms progress in a variable period and includes in cases from type 2 fibers to type 1: (i) enlargement of the sarcoplasmic reticulum; (ii) increase in oxidative properties, in mitochondrial subsarcolemmal proliferation and oxygen consumption; (iii) extends contraction and relaxation times and reduces calcium ATPase transport activity in the sarcoplasmic reticulum; and (iv) a reduction of fiber diameter and muscle mass occurs and, thus, changes to typical fiber type 1. The main molecular mechanisms involved corresponds to the function of one of the main developmental factors: (i) the Mef2 (myocyte enhancer factor-2) inhibition by histone deacetylase (HDAC); (ii) indirect phosphorylation of HDAC by calcium/calmodulin-dependent kinase; (iii) dephosphorylation of nuclear factor of activated T-cells (NFAT) by calcineurin; and (iv) changes in Six1 transcriptional complexes activation of slow muscle fiber genes (Sox6, HDAC4, Hrasls) and secondary changes in the expression of other genes associated to the thin and thick filament proteins (Myf2, Asp4, ACTN3, Eno3, Tnnt3, Srl, Tnnc2, Tnni2 [3, 20].

Conclusion

It is essential to know the main aspects of the normal skeletal muscle structure, development, plasticity, and regeneration. The various acquired and inherited myopathies relate to structural or functional disturbances, being essential to recognize the new pathophysiological mechanisms associated with these clinical conditions for proper clinical, histopathological, and genetic diagnosis and to provide new therapeutic approaches. Different regulatory mechanisms of formation, activity and structure of skeletal muscle have been described in recent years and represent the basis of what is believed to represent the basis for new therapeutic and diagnostic perspectives.

Compliance with Ethics Guidelines

Conflict of Interest Wladimir Bocca Vieira de Rezende Pinto, Paulo Victor Sgobbi de Souza, and Acary Souza Bulle Oliveira declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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