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REVIEW

Skeletal Muscle: A Brief Review of Structure and Function

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Abstract Skeletal muscle is one of the most dynamic and plastic tissues of the human body. In humans, skeletal muscle comprises approximately 40 % of total body weight and contains 50–75 % of all body proteins. In general, muscle mass depends on the balance between protein synthesis and degradation and both processes are sensitive to factors such as nutritional status, hormonal balance, physical activity/exercise, and injury or disease, among others. In this review, we discuss the various domains of muscle structure and function including its cytoskeletal architecture, excitation-contraction coupling, energy metabolism, and force and power generation. We will limit the discussion to human skeletal muscle and emphasize recent scientific literature on single muscle fibers.

Keywords Muscle actions · Metabolism · Force generation · Exercise · Sarcopenia · Dystrophy

Introduction

Skeletal muscle is one of the most dynamic and plastic tissues of the human body. In humans, skeletal muscle comprises approximately 40 % of total body weight, contains 50–75 % of all body proteins, and accounts for 30–50 % of whole-body protein turnover. Muscle is mainly composed of water (75 %), protein (20 %), and other substances including inorganic salts, minerals, fat, and carbohydrates (5 %). In general, muscle mass depends on the balance between protein synthesis and degradation and both processes are sensitive to factors such as nutritional status, hormonal balance, physical activity/exercise, and injury or disease, among others. The various protein compartments (structural, contractile, and regulatory) have received significant scientific attention because of their important contribution to mobility, exercise capacity, functioning, and health.

Skeletal muscle contributes significantly to multiple bodily functions. From a mechanical point of view, the main function of skeletal muscle is to convert chemical energy into mechanical energy to generate force and power, maintain posture, and produce movement that influences activity, allows for participation in social and occupational settings, maintains or enhances health, and contributes to functional independence. From a metabolic perspective, the roles of skeletal muscle include a contribution to basal energy metabolism, serving as storage for important substrates such as amino acids and carbohydrates, the production of heat for the maintenance of core temperature, and the consumption of the majority of oxygen and fuel used during physical activity and exercise. Of particular interest is the role of skeletal muscle as a reservoir of amino acids needed by other tissues such as skin, brain, and heart for the synthesis of organ-specific proteins [1]. Further, amino acid release from muscle contributes to the maintenance of blood glucose levels during conditions of starvation. Of relevance to disease prevention and health maintenance, a reduced muscle mass impairs the body's ability to respond to stress and chronic illness.

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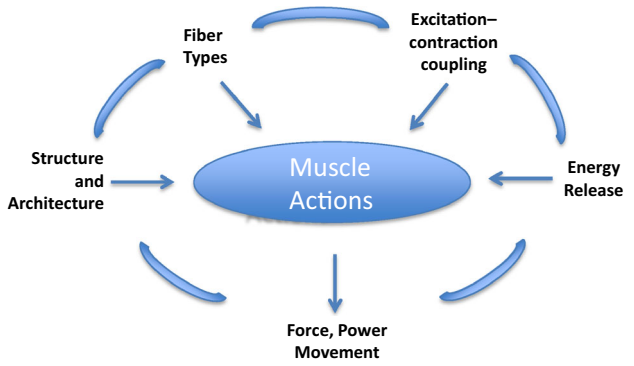

Fig. 1 Interacting skeletal muscle domains

During the last few decades, because of all of the above important functions of muscle, various techniques have been developed and used to quantify muscle mass, determine body composition, and study muscle function non-invasively. These techniques include the measurement of urinary creatinine concentration, ultrasonography, whole-body counting-neutron activation, computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy, bioelectrical impedance, and dual-energy X-ray absorptiometry (DEXA). An historical review of these methods has been recently published [2].

The present review will be limited to a description and discussion of human skeletal muscle (references to animal or in vitro models will be noted) with a general emphasis on factors that influence the nature of the various types of muscle actions responsible for force generation (Fig. 1). We will discuss the basic structural, physiological, and mechanical properties of muscle and emphasize recent scientific literature on single muscle fibers. The focus will be on limb muscles and the distinctive features of head and neck muscles such as the extraocular, middle-ear, and laryngeal muscles will not be discussed. To illustrate the dynamic nature of muscle tissue we will also use the exercise/inactivity paradigm, aging, and some pathological conditions as important conditions that induce significant acute and chronic changes and adaptations in skeletal muscle. Some of these factors are discussed in more detail in other articles included in this issue of the journal.

Basic muscle structure: from whole muscle to individual fibers

The architecture of skeletal muscle is characterized by a very particular and well-described arrangement of muscle fibers (also referred to as myofibers or muscle cells) and associated connective tissue. At the whole muscle level, the size of a muscle is determined mostly by the number and size of individual muscle fibers although pathological

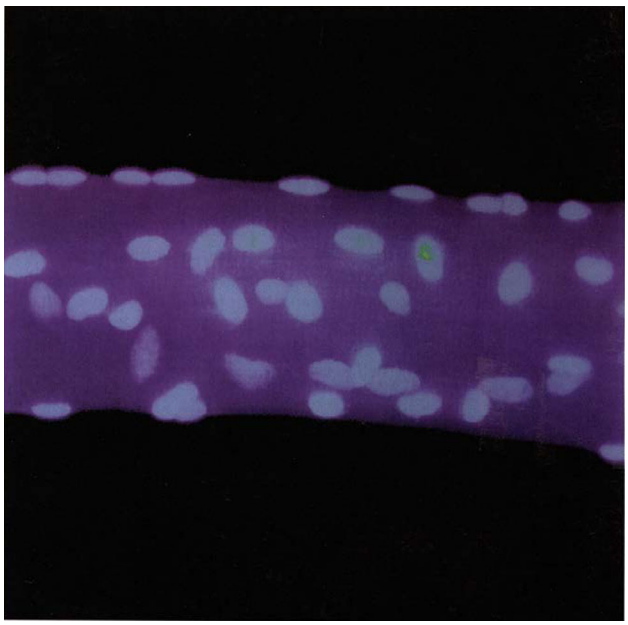

Fig. 2 Myonuclei along the length of a single muscle fiber stained with a fluorescent dye that binds to DNA and located with confocal microscopy (From: Allen et al. [81])

infiltration by fat and connective tissue may alter this relationship [3, 4]. Muscle fibers are multinucleated and post-mitotic (Fig. 2). For the most part each nucleus within a muscle fiber controls the type of protein synthesized in that specific region of the cell. These regions are known as nuclear domains and have a highly regulated, but not constant, size [5]. Protein expression in adjacent domains of a single fiber appears to be coordinated in such a way that the type of protein (i.e., myosin) produced is similar across the length of the fiber. However, this is not always the case and non-uniformity of contractile properties in adjacent segments of a single fiber has been reported [6]. Satellite cells are the adult stem cells of skeletal muscle. These cells are located between the sarcolemma and the basal lamina and contribute to muscle growth, repair, and regeneration [5, 7]. When activated by myogenic factors, satellite cells proliferate and differentiate into new muscle fibers [8].

An individual muscle is surrounded by a layer of connective tissue known as the epimysium (Fig. 3). Group of fibers within that muscle are arranged in bundles and surrounded by another layer of connective tissue known as the perimysium. A single muscle fiber (with approximate dimensions of 100 μm in diameter and 1 cm in length) is surrounded by a cell membrane or sarcolemma. Associated with the sarcolemma there is a complex of several proteins that is physically connected to the internal myofilament structure; particularly to the actin protein present in the thin filament. The absence (partial or complete) or dysfunction of one of these proteins may result in damage to the

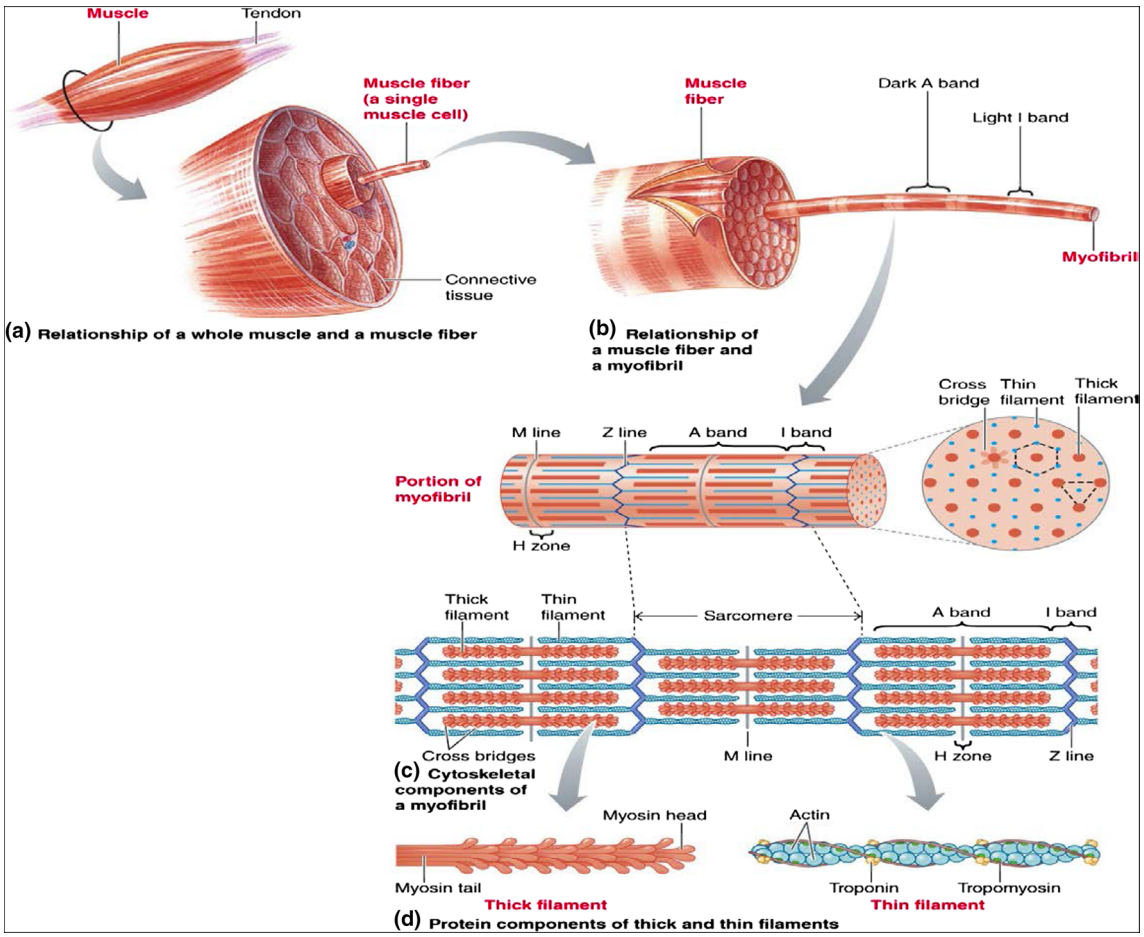

Fig. 3 Structure of skeletal muscle (From: Raven et al. [82, Fig. 3.6]; original in Sherwood [83, Fig. 8.2])

sarcolemma, muscle weakness, and atrophy. For example, this complex is the location of the protein dystrophin that is partially or completely absent in some types of neuromuscular disorders such as Duchenne and Becker muscular dystrophies [9].

Muscle Proteins

Not considering their water content, single muscle fibers are made mostly (~80 %) of protein (contractile, regulatory, cytoskeletal) and sarcoplasm (~8 %) [10]. The study of muscle proteins has advanced considerably in the last few decades with the use of modern proteome analysis techniques. This topic has been recently reviewed [11, 12]. It is estimated that each muscle fiber is made of thousands of myofibrils and contains billions of myofilaments (Fig. 3). When assembled together, in a very orderly and characteristic pattern, the myofilaments form sarcomeres, which are the basic contractile units of skeletal muscle. The two most abundant myofilaments (proteins) are actin and myosin comprising approximately 70–80 % of the total protein content of a single fiber. Myosin is the main molecular motor and a total of eleven sarcomeric myosin genes with their corresponding protein products have been described in mammals (some may not be expressed in humans). Two of these genes are also expressed in cardiac muscle. The sarcomere and sarcoplasm contain many other proteins that contribute to the structure of the cytoskeleton, coupling of the excitation and contraction processes, energy release, and the generation of force and power [13]. Of particular relevance are regulatory proteins such as the calcium-dependent troponin complex (including troponins C, I, and T), and tropomyosin that are associated with the actin filament and play very important roles in the activation process that leads to myofilament sliding and force generation (see below).

Other proteins that contribute to the mechanical and physiological properties of muscle are titin and nebulin [13, 14]. Titin is a large elastic protein that attaches to the Z disk of the sarcomere and to myosin and helps to stabilize and align the thick filament. Nebulin, on the other hand, is

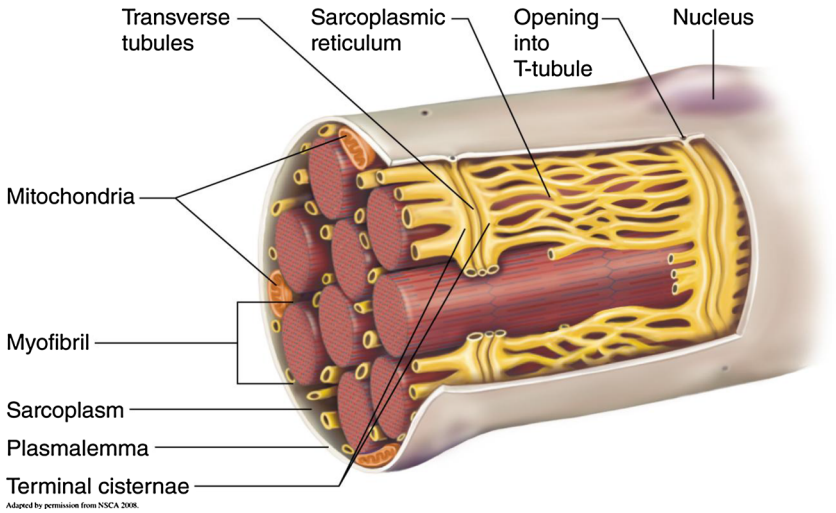

Fig. 4 The transverse tubules and sarcoplasmic reticulum systems. Adapted, by permission, from G.R. Hunter and R.T. Harris, 2008, Structure and function of the muscular, neuromuscular, cardiovascular, and respiratory systems. In Essentials of strength training and conditioning, 3rd ed., edited for National Strength and Conditioning Association by T.R. Baechle and R.W. Earle (Champaign, IL: Human Kinetics), 5

integrated with other proteins in the thin filaments containing actin [13]. These proteins contribute to the integrity of the sarcomere, influence passive tension and stiffness characteristics of single cells, and may be relevant to the assembly of myofibrils and cell signaling. Further, in vitro experiments suggest that titin may contribute to the generation of force during muscle actions [14, 15]. The Z disk of the sarcomere contains several proteins including α-actinin and serves as an attachment point for the actin myofilament. Other proteins connect the Z disk (for example desmin) to the sarcolemma and extracellular matrix as noted above and may be dysfunctional in some myopathies.

Muscle Fiber Organelles

Other cellular elements in the sarcoplasm of muscle fibers include a transverse tubular system (T tubule), the sarcoplasmic reticulum, and a mitochondrial network; the exact amount of these elements may depend on the fiber type (see below) (Fig. 4). The T tubule system is an invagination of the sarcolemma whose important role is the conduction of the nerve action potential to the interior of the cell [16]. This network of tubules is in contact with the exterior of the cell and ensures that excitation can spread uniformly throughout the fiber. Dysferlin is an important protein localized in the membrane of the T tubule system and is sensitive to changes in the calcium concentration within the cell [17].

The sarcoplasmic reticulum is responsible for the storage, release, and reuptake of calcium after activation (see below). The calcium is stored in the terminal cisternae (ends of the sarcoplasmic reticulum) that are in close contact with the transverse tubule system. The two cisternae on both sides of the T tubule together form a structure known as the triad (two cisternae plus one tubule) [18]. Two types of proteins in the sarcoplasmic reticulum contribute to maintaining calcium homeostasis; the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and calsequestrin. The former is responsible for the calcium reuptake into the cisterna after muscle activation and the latter binds calcium loosely within the sarcoplasmic reticulum.

Mitochondria form a three-dimensional network throughout the cell (as opposed to the old concept of isolated organelles) that generates the energy needed for muscle actions when oxygen is made available to the muscle fiber [19]. Some mitochondria are located closer to the sarcolemma reducing the diffusion distance for oxygen transported by the capillary supply. This is particularly useful during aerobic (or endurance) exercise when the demand for oxygen increases. Another population of mitochondria is located in the inter-myofibrillar space.

It is known that various stimuli such as exercise training and aging as well as various neuromuscular pathologies induce significant changes in the structure and function of the cellular elements mentioned above (see sections below for detailed discussion). For example endurance exercise training induces mitochondrial biogenesis, a process that is regulated by the peroxisome proliferator-activated receptor-γ coactivator-1α [20]. Both, the number and size of mitochondria increase with training programs of endurance/aerobic type of exercise. On the other hand, aging muscle has a fragmented sarcoplasmic reticulum that impairs calcium release and muscle activation [21]. This may contribute to muscle weakness in this population. Finally, congenital and acquired neuromuscular diseases such amyotrophic lateral sclerosis and chronic conditions such as the metabolic syndrome and obesity are associated with abnormalities in the mitochondrial network.

Heterogeneity of Muscle Tissue: Muscle Fiber Types

The heterogeneity of human skeletal muscle is illustrated by the significant variability in the biochemical, mechanical, and metabolic phenotypes of individual fibers. In the human body, different muscles have different relative predominance of the various fiber types. The presence of fibers with different properties in the same muscle may reflect an adaptation to different patterns of activity imposed by the motor neurons. This diversity of physiological properties is a very important property because it allows the participation of a muscle in activities with various metabolic and mechanical demands. The architecture of capillary supply networks that supports these metabolic demands varies depending on the fiber type [22]. Further, the response of muscle fibers to stimuli such as denervation, corticosteroids, hormonal levels, aging, inactivity, and disease is fiber type specific. For example, more atrophy is noted in type II fast fibers than in type I slow fibers in conditions associated with muscle wasting such as cancer. Two very comprehensive reviews of fiber diversification, including muscles of several mammalian species, have been published recently [23, 24]. The study and understanding of the properties of individual fibers have been facilitated by the use of the percutaneous muscle biopsy [25] in combination with histochemical and immunological methods, the development of the permeabilized single muscle fiber technique [26] for the study of human fibers, and recent advances in proteomics.

During the last few decades, muscle fibers have been classified using different criteria including the: (1) color of muscle fibers (red vs. white) that correlates with myoglobin content, (2) contractile properties of the motor units in response to electrical stimulation, (3) speed of shortening during a single twitch (fast vs. slow), (4) degree of fatigability during sutained activation (fatigable vs. fatigue-resistant), (5) predominance of certain metabolic or enzymatic pathways (oxidative vs. glycolytic), (6) enzyme-histochemical stain reaction (based mainly on ATPase staining techniques but also on oxidative enzymes such as succinate dehydrogenase or SDH), (7) calcium handling by the sarcoplasmic reticulum (slow vs. fast) [18], and (8) protein isoform expression, among others [24]. The speed of contraction correlates with the extent of development of the sarcoplasmic reticulum while the tolerance to fatigue and oxidative capacity correlates with the mitochondrial content. The most frequently used classification for adult human limb muscles includes three fiber types: type I (slow, oxidative, fatigue-resistant), IIA (fast, oxidative, intermediate metabolic properties), and IIx (fastest, glycolytic, fatigable). Humans also express, under various conditions and in specific muscles, other types of myosin such as embryonic, neonatal, and extraocular (see Ref. [23] for a detailed description and discussion).

The identification of muscle protein isoforms has become an important approach used by investigators in the field to distinguish muscle fiber types. Further, with the use of techniques such as protein electrophoresis and immunereactivity to antibodies it has been demonstrated that a single muscle fiber may express, simultaneously, more than one type of myosin heavy chain; for example type I and IIa or IIa and IIx together. A shift in the expression of myosin heavy chain along the length-axis of a single fiber can result from the transcription of different mRNA's in different nuclear domains. These so-called hybrid fibers have been shown to increase with exercise, aging [27], and in some pathological conditions. Isoforms of many muscle proteins other than myosin have been identified and associated with specific muscle fiber types [12]. For example slow and fast troponin T isoforms are known to exist in type I and II fibers, respectively [23]. Several myogenic transcription factors such as MyoD and myogenin play a significant role in the synthesis of muscle proteins that are specific for each of the fiber types. This process of fiber differentiation is influenced also by factors external to muscle such as the levels of thyroid hormones and the activity pattern of peripheral nerves.

Excitation–Contraction Coupling: Physiology of Muscle Activation

Excitation–contraction (EC) coupling is the coordination of two processes that are needed for the generation of force; the transmission of the nerve stimulus to the triad followed by the release of calcium from the cisternae of the sarcoplasmic reticulum and the interaction between actin and myosin that forms cross-bridges. Many (but not all) of the molecular events during E–C coupling have been defined. Briefly, the action potential that arrives to the muscle fiber membrane is conducted to the interior of the muscle cell via the transverse tubular (T tubule) system. The nervous impulse arrives in the triad where the T tubule is in close proximity with the terminal cisternae of the sarcoplasmic reticulum that stores calcium. A voltage sensor subunit of the dihydropiridine receptors on the T tubule opens and allows an inward current of calcium [28]. This calcium current triggers the opening of the ryanodine receptors in the terminal cisternae of the sarcoplasmic reticulum and releases large amounts of calcium into the sarcoplasm. The calcium released into the sarcoplasm then binds to the regulatory protein troponin C on the actin thin myofilament. This initiates a series of molecular events that displace the tropomyosin blocking the active site of the actin filament.

A detailed description and discussion of the events that follow is beyond the scope of this brief review. Suffice it to say that the exposure of the active site on actin allows the binding of the head of the myosin molecule with actin. ATP and the ATPase located in the myosin head, facilitate the detachment of myosin from actin (a cross-bridge formed in a previous contraction) and the formation of a new cross-bridge. The detailed structure of the myosin head was described for the first time in 1993 [29] and contributed significantly to our understanding of the mechanics and physiology of this process. As mentioned above, the end-result of this sequence of events is the sliding of the actin and myosin filaments and the generation of force. Recent evidence suggests that this sequence of events within the cell is modulated by several genes including MTMR14, MG29, and KLF15 [30].

Energy Production and Release

All muscle actions require energy in the form of ATP. The metabolic energy pathway used to produce and sustain muscle actions depends on the duration and intensity of the activity. The three basic energy pathways in the muscle fiber are stores of ATP and CP, anaerobic glycolysis, and oxidative phosphorylation. The first supports high intensity short duration (few seconds) activities because the amount of ATP and CP reserves in muscle fibers is small. Anaerobic glycolysis produces ATP quickly to sustain muscle actions for a couple of minutes but the end products (H^+, lactate) impair muscle function and are associated with muscle fatigue. Finally, the energy for exercise performed at intensities that can be sustained for longer duration (minutes to hours) is supplied by oxidative phosphorylation within the mitochondrial network. A network of capillaries transports oxygen to the active muscle fibers. The extent of this network correlates with the metabolic demand on the muscle fiber. The architectural relationship between these two structures was described very early in the twentieth century by August Krogh and recently discussed [31]. It is important to note that the utilization of these metabolic pathways is not an "all or none" phenomenon. Pathways overlap and can be activated at different points in time during a single session of exercise depending on the intensity of the effort.

Carbohydrates (plasma glucose and muscle glycogen) and fats (plasma free fatty acids and muscle triglycerides) are the two main fuels utilized by the muscle cell to produce ATP [32]. Metabolism of amino acids may contribute a small percentage of the total energy production. Again, the selection of the specific fuel depends on the intensity and duration of the exercise. In general, at high intensities, muscle actions are mainly fuelled by muscle glycogen stores. On the other hand, lower intensity and long duration exercise utilizes the metabolism of free fatty acids for most of the energy needs. In real life, most activities activate different pathways at different points in time and use a combination of fuels to produce the ATP needed for muscle actions.

Types of Muscle Actions

Muscle activation results in muscle actions that can be classified into three basic types: static, dynamic concentric, and dynamic eccentric. A static (also known as isometric) muscle action is characterized by the generation of force in the absence of movement of the joint or limb. Under these conditions, the resistance is higher than the force generated (i.e., pushing against a wall). On the other hand, a dynamic action involves force generation and joint movement. Dynamic (previously known as isotonic) actions can be divided into concentric or eccentric actions. Concentric muscle actions result in the shortening of a muscle because its origin and insertion come closer together (i.e., flexing the elbow). Eccentric actions result in the lengthening of the muscle because its origin and insertion move farther apart (i.e., lowering a load from a bent elbow position). A type of dynamic action produced in the laboratory using a special device is known as isokinetic because the velocity of the movement is constant. This type of muscle action is artificial and does not occur in normal human movement because during the performance of daily activities there is a combination of acceleration and deceleration.

Eccentric muscle actions, if not performed carefully, can be associated with muscle damage [33]. However, exercise training, particularly training that includes eccentric actions, attenuates this damage and the associated inflammatory response. In the rehabilitation of patients with cardio-pulmonary disease, these types of muscle action are very useful because, at a given level of force, eccentric actions are associated with a lower level of muscle activation (as determined by electromyography), energy consumption, and oxygen consumption.

Force Generation and Movement

The theory that explains the basic mechanism by which a muscle fiber generates force was proposed in 1954. That theory is known as the sliding filament theory and continues to be, with some modifications, the accepted explanation for the generation of force [34, 35]. The force generated by individual actin–myosin cross-bridges is transmitted longitudinally and laterally within the fiber. Of particular importance is the transmission of force to the Z

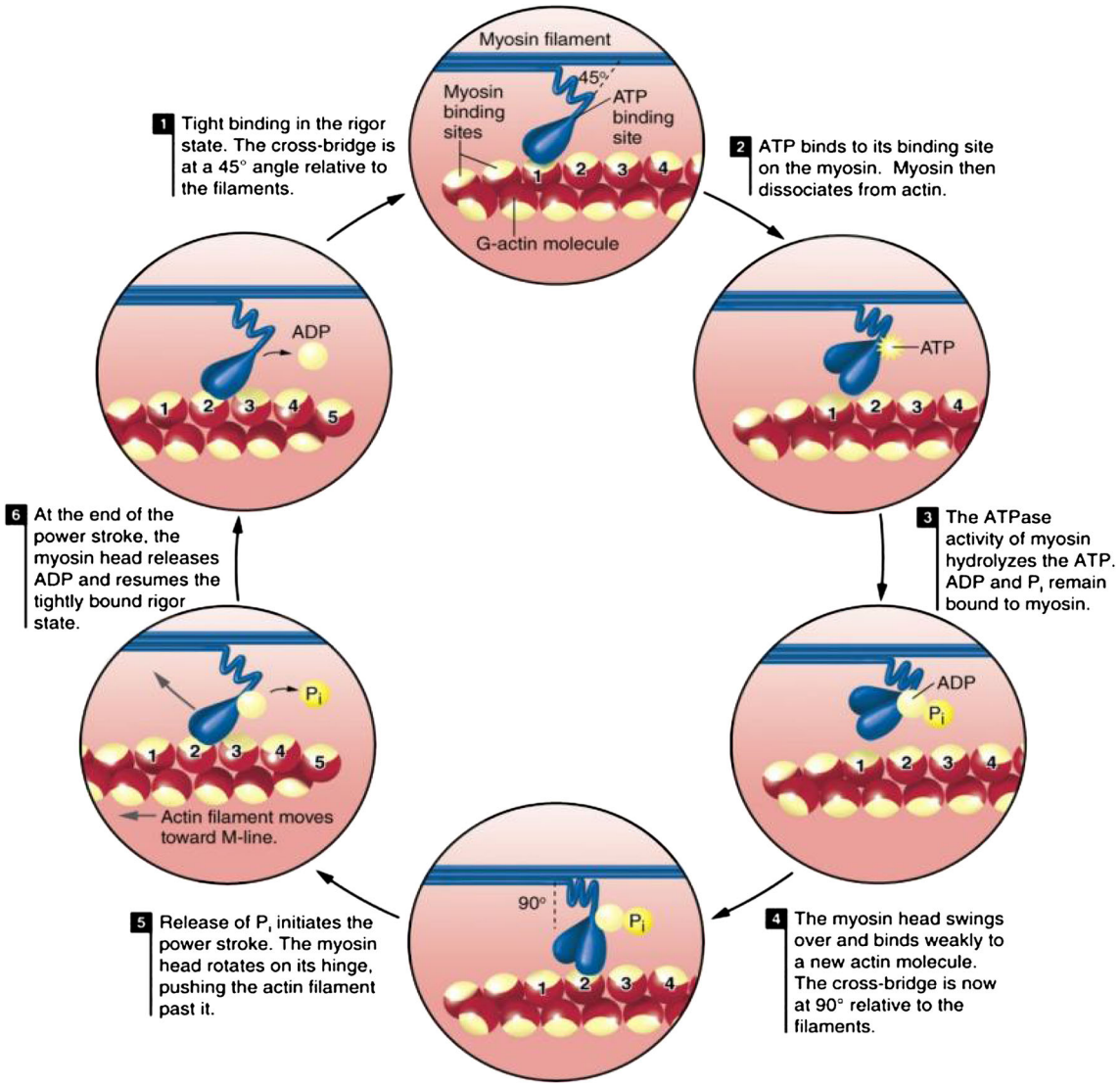

Fig. 5 Sequence of events leading to the generation of force and power. Reprinted, by permission, from W.L. Kenney, J.H. Wilmore, and D.L. Costill, 2012, Physiology of sport and exercise, 5th ed. (Champaign, IL: Human Kinetics), 36 (adapted from Unglaub Silverthorn, Human Physiology, Fig. 12.9, Pearson Education Inc., 2007)

disk of the sarcomeres in series. Movement is finally produced when the force reaches the myotendinous junction, tendons, and joints.

The force generated by a muscle depends on many factors including the degree of activation by the nervous system, its architecture (including the angle at which muscle fibers insert into the tendon known as pennation angle), the muscle size, the space between myofilaments, the number of actin–myosin cross-bridges formed, the force generated by each cross-bridge, and the quality of the interaction between the cellular elements (see above). With regards to the latter, researchers in the field have realized that the correlation between muscle strength and size is not unity suggesting that other factors contribute to force production. The force generated by a muscle adjusted for its size is known as specific force and has been accepted as an indicator of muscle quality. It is known that this property is reduced in older humans (see below) and with denervation.

Briefly, the series of events that result in the generation of force begins when ATP is made available to an existing actin–myosin cross-bridge and (Fig. 5). ATP binds to its binding site on the myosin head. The ATPase, also in the myosin head, hydrolyzes the ATP resulting in ADP and Pi and in the detachment of the existing cross-bridge. The myosin head swings over and binds to a new actin molecule. Release of Pi triggers a power stoke and myosin pushes the actin filament pass it. Force is generated during this power stroke. At the end of the power stroke, ADP is released and myosin remains bound to actin in rigor. Cross-

bridges exist in two states, weak-binding and strong-binding state. As the name implies, the latter is a more important contributor to force generation and more cross-bridges exist in this state during maximal muscle activation. In this model, total ATP consumption depends on the total number of myosin heads, the fraction of myosin heads forming cross-bridges, and the apparent rate constant for cross-bridge detachment. The rate of consumption of ATP is a reflection of the myosin heavy chain isoform expression and, in humans, it is lowest in type I fibers, intermediate in IIa fibers, and maximal in IIx fibers [36].

The amount of force generated also depends on several basic biomechanical properties of the musculoskeletal system. For example, force depends on the length of the muscle or sarcomere (directly related to the position of the limb) upon activation. This property is known as the force–length relationship. At lengths longer and shorter than the optimal length, the force generated after activation is lower because the overlap between actin and myosin needed for cross-bridge formation is sub-optimal. From a practical point of view, this means that the performance of daily activities is dependent on the angular position of the joint; in other words, carrying heavy objects with the upper limbs is usually done with the elbows at 90° of flexion because it optimizes actin–myosin overlap.

The generation of force also depends on the velocity of the movement. This relationship is known as the force–velocity curve. During concentric muscle actions (when the muscle shortens), an increase in the velocity of movement results in lower force. Similarly, muscle actions against high loads can only performed at relatively slower velocities. On the other hand, during eccentric muscle actions (when the muscle is lengthening), an increase in velocity results in higher force. This is the reason why strengthening exercises that include eccentric muscle actions are frequently and effectively used during the rehabilitation of musculoskeletal injuries. Finally, the power produced by an active muscle depends on the force generated (power–force curve) and the velocity of movement (power–velocity curve). Power is low at low forces and increases to a maximal level at approximately 40 % of the maximal force. On the other hand, power is low at slow velocities and increases to a maximum that depends on the muscle fiber type (see above) and is approximately 15–20 % of the maximal velocity.

Force can be measured in vivo using force transducers, free weights, and different commercially available dynamometers. A clinically useful measurement of strength (defined as the maximal force generated at a specific velocity) is the one repetition maximum (1RM), which is the maximal amount of weight that can be lifted only once throughout the full range of motion of a joint. Because of the potential learning effect, this test is more reliable when administered after significant practice or familiarization. More than one testing session may be required. The ability of human single fibers and single myosin molecules to generate force has also been measured in vitro [37, 38]. These studies show that type I myosin isoform (slow) produces less force than type II myosin isoform (fast). However, no differences among sub-types of fast myosin (IIa, IIx, or hybrid IIax) were reported. The level of force generated during muscle actions is influenced by the concentration of calcium in the sarcoplasm and the sensitivity of the thin filament containing troponin and actin. This relationship is known as the force–Ca^{2+} curve.

Exercise: Adaptations to Training

The previous sections described the various cellular and physiological changes during muscle actions under conditions typical of a single acute bout of exercise. On the other hand, exercise training is characterized by the regular and frequent repetition of bouts of certain intensity and duration (see related article in this issue). Training induces in muscle significant structural and metabolic changes that are exercise-type specific. Several signaling pathways activated during exercise have been identified that contribute to skeletal muscle growth and adaptation [39]. Although multiple combinations of different types of exercise are possible, we will briefly describe adaptations to endurance (also known as aerobic or cardiovascular) training and strength (also known as resistance) training because these two types of training have been extensively studied and are used frequently in clinical settings.

Endurance exercise involves the activation of large muscle groups at an intensity that allows an individual to sustain the activity for prolonged periods of time without undue fatigue. This intensity requires a highly efficient oxygen transport and delivery chain. Typical activities included under this definition are walking, running, swimming, some types of dancing, cycling, and some team sports. Muscle adaptations to this type of training at the level of cellular proteins have been recently reviewed [40]. Briefly, the capillary supply to active muscles increases to facilitate oxygen delivery and the number and size of mitochondria, particularly those located in close proximity to the sarcolemma increases [20]. Fat and glycogen storage is enhanced to fuel muscle actions and the concentration of several oxidative enzymes of the Krebs cycle needed for the aerobic production of ATP is increased. Endurance trained muscles have a more developed sarcoplasmic reticulum and show downregulation of specific types of calcium handling proteins such as SERCA (see above) suggesting an increase in muscle fiber efficiency [41]. The

hallmark of this type of exercise training is an enhanced metabolic capacity. However, endurance training is not typically associated with changes in muscle size or force-generating capacity.

Strength training results in an increased capacity to generate force, partially due to muscle hypertrophy. In humans, it has been shown that the main cause for hypertrophy is an increase in the size of individual muscle fibers due to increases in protein synthesis and the addition of myofilaments, myofibrils, and sarcomeres. This may result from activation and fusion of satellite cells resulting and the addition of new myonuclei. Similar to endurance training, several factors and molecular pathways that regulate muscle mass and the hypertrophic response have been identified [42]. Signaling pathways are activated after a bout of resistance exercise in young and old humans [43]. The role of two important signaling pathways has been recently reviewed [44, 45]. In one of these pathways insulin-like growth factor-1 binds to its receptor on the sarcolemma and induces the activation of the Akt protein. Akt activates mammalian target of rapamycin (mTOR) that regulates factors that control protein synthesis. This pathway can be activated also by calcium and mechanical activity. In a second pathway, myostatin (a member of the TGF-β superfamily), acts as a negative regulator of muscle mass. Therefore, mutations of the myostatin gene or blocking of this pathway results in muscle hypertrophy. Several microRNA's have been identified as important participants in the regulation of muscle mass [45] by intervening in these two pathways.

Changes in muscle mass may result in a lower concentration per muscle area unit (but not number) of capillaries and other cellular elements. In both mice and humans, the activation of satellite cells could play an important role in the hypertrophic response [46]. Furthermore, several genes are activated during an acute bout of strengthening exercise training that contribute to muscle growth and this genetic response that leads to muscle hypertrophy is modulated by training [47]. In order to stimulate muscle hypertrophy with exercise, dietary considerations are important. A recent meta-analysis shows that the gains in muscle mass and strength with strength training can be augmented by protein supplementation in both young and older volunteers [48]. It is interesting that amino acids activate the same IGF-1 signaling pathway activated by strength training mentioned in the previous paragraph.

Aging and Sarcopenia

One of the most distinctive features of aging is the presence of muscle weakness and atrophy. The term sarcopenia was used for the first time by Rosenberg [49, 50] to refer to the loss of lean body mass with aging (see related article in this issue). More recently, the European Working Group on Sarcopenia in Older People has expanded the definition and suggested criteria for diagnosis [51] including the presence of a lower muscle mass (as determined for example by bioelectrical impedance or DEXA) and the presence of muscle weakness and/or impaired performance (slow walking speed). The prevalence of sarcopenia in the older population has been reported to range between 4 and 27 % depending on the study, gender, and country. The loss of muscle mass and strength in older people is of greater magnitude in longitudinal studies when compared to cross-sectional observations [52]. More muscle mass and strength is lost by men compared to women and in the lower limbs compared to the upper limbs [52, 53]. It must be noted that the loss of strength with advancing age is not a universal phenomenon and some individuals have maintained muscle strength after 10 years of follow-up [54]. This selective preservation of muscle strength may be associated with the daily level of physical activity of the study population. Sarcopenia may also be associated with the loss of muscle power (force × velocity), particularly in older people with mobility limitations [55]. Power correlates very well with function and its loss is a good predictor of mobility limitations and falls.

At the level of the individual muscle fiber, sarcopenia may be associated with a reduced number of satellite cells; especially those associated with fibers expressing type II (fast) myosin heavy chain [56]. This is relevant because most of the motor unit and fibers lost with advanced adult age are type II. Moreover, the satellite cell activation in response to muscle damage is blunted in older adult men; a phenomenon that is mediated by interleukin-6 [57]. Aging muscle is also characterized by alterations in other components of the muscle cell. For example, alteration in the structure of the sarcoplasmic reticulum results in segregated calcium stores that impair the efficiency of the EC coupling [21]. Another example of the age-related alterations in cell organelles is the loss of mitochondria [58]. Aging is associated with a loss of mitochondrial content and function that is influenced by the level of physical activity and can be partially reversed by exercise training.

A reduction in muscle size is a contributor to sarcopenia but is not the only (and may not be the most important) explanation for it. Changes in muscle fiber quality have been reported by several investigators including our group [37]. The importance of age-related changes at the level of the myofilaments has been recently discussed [59]. The majority of studies demonstrate that older men and women have reduced single fiber maximal force even after adjustments for variability in fiber size. This is true in both type I and II fibers. Many molecular mechanisms have been

proposed to explain such dysfunction including a reduction in myosin protein content; this may be particularly true in immobilized muscle [60]. The latter may be related to gene transcription with abnormalities in the myostatin gene or reductions in translation and protein synthesis leading to a lower myosin concentration per unit of muscle cell area. In addition, post-translational modifications of myosin via mechanisms such as oxidation and glycosylation may result in myofilament dysfunction. Oxidative modification of myosin may disrupt the binding of the myosin head to the actin filament and, thus, reduce the number of actin–myosin cross-bridges in the strong-binding state [61]. This will limit force and power generation. It is interesting that longitudinal studies suggest that clusters of fibers that are not lost during aging try to compensate for these age-related differences in fiber size and quality [55, 62, 63] and although whole muscle performance is reduced, single muscle fiber properties may be relatively well preserved.

Other mechanical properties are also altered in older human muscle. An increased in instantaneous stiffness (reduction in elasticity) has been reported in whole muscle as well as in single fibers [64]. This may be due to an increase in the number of cross-bridges in the weak-binding state but other factors such as changes in cross-bridge compliance and sarcomeric elements like titin may contribute. As previously noted, the role of this important protein in muscle actions has been recently reviewed [65]. In conclusion, independent of the mechanism(s) limiting normal myofilament interaction substantial evidence supports the idea that muscle impairment in older people is, at least partially, a qualitative and not a quantitative problem.

Inactivity and Bed Rest

One interesting question that requires more research is whether the age-related alterations described above are directly due to the aging process or mainly to disuse. Indeed, with advanced age, the level of physical activity decreases and may be responsible, at least partially, for the alteration of muscle fiber quality and for muscle wasting/weakness in general. In fact, recent evidence shows that the incidence of sarcopenia in both older men and women is lower in those that have a higher level of physical activity [66]. The current experimental human model of physical inactivity is strict bed rest, 24 h a day, in a head-down (−6°) position [67]. Studies aiming at simulating microgravity/space flight have use this model extensively. Short studies of 2, 8, and 12 days of bed rest have not reported significant effects on muscle mass or strength [68]. On the other hand, longer periods of rest (35 or 90 days) induce a large decrease in force and power generating capacity of muscles of the lower limbs [69, 70]. A major contributor to such impairments is muscle atrophy affecting both type I and II fibers [71]. Atrophy is defined as a decrease in size due to a loss of organelles, cytoplasm, and/or protein.

As mentioned above, muscle size is determine by the delicate balance between protein synthesis and degradation. Bed rest studies tend to demonstrate that proteolysis pathways are up-regulated as attested by the increased activation of the ubiquitin–proteasome pathway and autophagy after 35 days of rest. Similar to the situation in sarcopenia, long periods of bed rest lead to a loss of strength exceeding the loss of mass. This suggests that a change in muscle quality occurs. The reduction in quality cannot be explained on the basis of fat or connective tissue infiltration [72] and is probably due to an alteration of the quality of the contractile elements at the single fiber level. Indeed, force, velocity, and power are all severely affected in both type I and II cells [71] with bed rest. The molecular mechanisms underlying these changes remain unclear but are likely to include the disruption of actin–myosin cross-bridges caused by unusual post-translational modifications of myosin such as increased phosphorylation and *O*-*N*-acetyl glucosaminylation [73]. It is important to point out that, despite these similarities, there are differences between sarcopenia and bed rest. For instance, a shift toward a faster muscle fiber type composition (increased type II to type I fiber ratio) is commonly reported after long periods of bed rest [71] whereas the opposite tends to happen during the aging process. It appears that physical inactivity results in complex changes that may be influenced by environmental conditions.

Muscle Fiber Function in Myopathies

One of the most common groups of diseases affecting the skeletal muscles is the group of muscular dystrophies. These are caused by mutations in genes encoding for proteins involved in the dystrophin–glycoprotein complex or enzymes that cause post-translational modifications of such proteins [74]. Patients experience early and disabling progressive limb muscle weakness. The cellular and molecular mechanisms underlying such functional impairment remain elusive but are likely to be related to muscle fiber degeneration [74]. Very few studies have examined the underlying pathophysiology of these disorders at the level of muscle fibers in humans. Most published studies are limited to the use of animal models. Of interest, genetic mutations in the dystrophin–glycoprotein complex are associated with a reduction in the sliding velocity of actin myofilaments on myosin [75] and with alterations in type I and II muscle fiber force and quality [76, 77]. These alterations can only result in impaired functional capacity.

In addition to the muscular dystrophies, some congenital muscle diseases are associated with impaired fiber function. This is the case in disorders related to mutations in genes encoding for the regulatory protein tropomyosin [78]. For instance, the missense mutation R133W located in the mid-region of the tropomyosin segment induces muscle weakness mainly via changes in muscle fiber force and quality [79, 80]. Indeed, by recording X-ray diffraction patterns of human isolated membrane-permeabilized fibers, our group has been able to prove that the mutation partially blocks tropomyosin movement over the actin filaments, limiting the binding of numerous myosin heads [80]. This induces a shorter duty ratio, as myosin molecules seem to spend a reduced fraction of the ATPase cycle strongly bound to actin [77]. It is likely that future studies will reveal the nature of the alterations at the cellular and molecular levels in many of these disorders of skeletal muscle.

Concluding Statement

Skeletal muscle is a very dynamic tissue with a cellular composition and architecture designed to support mobility and facilitate human function. Many advances have been made in understanding the structure of skeletal muscle at the cellular and molecular levels as well as the three physiological domains of EC coupling, energy metabolism, and force generation. Further investigations are needed to explore the integration of these domains and their regulation at the genetic level. Research on the adaptations of skeletal muscle to exercise, aging, bed rest, and disease will help us understand the underlying mechanisms of plasticity.

Conflict of interest Walter R. Frontera and Julien Ochala declare 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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