Section 1
Strength and Conditioning Biology

1.1 Skeletal Muscle Physiology

Valmor Tricoli, University of São Paulo, Department of Sport, School of Physical Education and Sport, São Paulo, Brazil

1.1.1 INTRODUCTION

The skeletal muscle is the human body's most abundant tissue. There are over 660 muscles in the body corresponding to approximately 40–45% of its total mass (Brooks, Fahey and Baldwin, 2005; McArdle, Katch and Katch, 2007). It is estimated that 75% of skeletal muscle mass is water, 20% is protein, and the remaining 5% is substances such as salts, enzymes, minerals, carbohydrates, fats, amino acids, and high-energy phosphates. Myosin, actin, troponin and tropomyosin are the most important proteins.

Skeletal muscles play a vital role in locomotion, heat production, support of soft tissues, and overall metabolism. They have a remarkable ability to adapt to a variety of environmental stimuli, including regular physical training (e.g. endurance or strength exercise) (Aagaard and Andersen, 1998; Andersen *et al.*, 2005; Holm *et al.*, 2008; Parcell *et al.*, 2005), substrate availability (Bohé *et al.*, 2003; Kraemer *et al.*, 2009; Phillips, 2009; Tipton *et al.*, 2009), and unloading conditions (Alkner and Tesch, 2004; Berg, Larsson and Tesch, 1997; Caiozzo *et al.*, 2009; Lemoine *et al.*, 2009; Trappe *et al.*, 2009).

This chapter will describe skeletal muscle's basic structure and function, contraction mechanism, fibre types and hypertrophy. Its integration with the neural system will be the focus of the next chapter.

1.1.2 SKELETAL MUSCLE MACROSTRUCTURE

Skeletal muscles are essentially composed of specialized contracting cells organized in a hierarchical fashion supported by a connective tissue framework. The entire muscle is surrounded by a layer of connective tissue called fascia. Underneath the fascia is a thinner layer of connective tissue called epimysium which encloses the whole muscle. Right below is the perimysium, which wraps a bundle of muscle fibres called fascicle (or fasciculus), thus; a muscle is formed by several fasciculi. Lastly, each muscle fibre is covered by a thin sheath of collagenous connective tissue called endomysium (Figure 1.1.1).

Directly beneath the endomysium lies the sarcolemma, an elastic membrane which contains a plasma membrane and a basement membrane (also called basal lamina). Sometimes, the term sarcolemma is used as a synonym for muscle-cell plasma membrane. Among other functions, the sarcolemma is responsible for conducting the action potential that leads to muscle contraction. Between the plasma membrane and basement membrane the satellite cells are located (Figure 1.1.2). Their regenerative function and possible role in muscle hypertrophy will be discussed later in this chapter.

All these layers of connective tissue maintain the skeletal muscle hierarchical structure and they combine together to form the tendons at each end of the muscle. The tendons attach muscles to the bones and transmit the force they generate to the skeletal system, ultimately producing movement.

1.1.3 SKELETAL MUSCLE MICROSTRUCTURE

Muscle fibres, also called muscle cells or myofibres, are long, cylindrical cells 1–100 μm in diameter and up to 30–40 cm in length. They are made primarily of smaller units called myofibrils which lie in parallel inside the muscle cells (Figure 1.1.3). Myofibrils are contractile structures made of myofilaments named actin and myosin. These two proteins are responsible for muscle contraction and are found organized within sarcomeres (Figure 1.1.3). During skeletal muscle hypertrophy, myofibrils increase in number, enlarging cell size.

A unique characteristic of muscle fibres is that they are multinucleated (i.e. have several nuclei). Unlike most body cells, which are mononucleated, a muscle fibre may have 250–300 myonuclei per millimetre (Brooks, Fahey and Baldwin, 2005; McArdle, Katch and Katch 2007). This is the result of the fusion of several individual mononucleated myoblasts (muscle's progenitor cells) during the human body's development. Together they form a myotube, which later differentiates into a myofibre. The plasma membrane of a muscle cell is often called sarcolemma and the sarcoplasm is equivalent to its cytoplasm. Some sarcoplasmic organelles such as the sarcoplasmic reticulum and the transverse tubules are specific to muscle cells.

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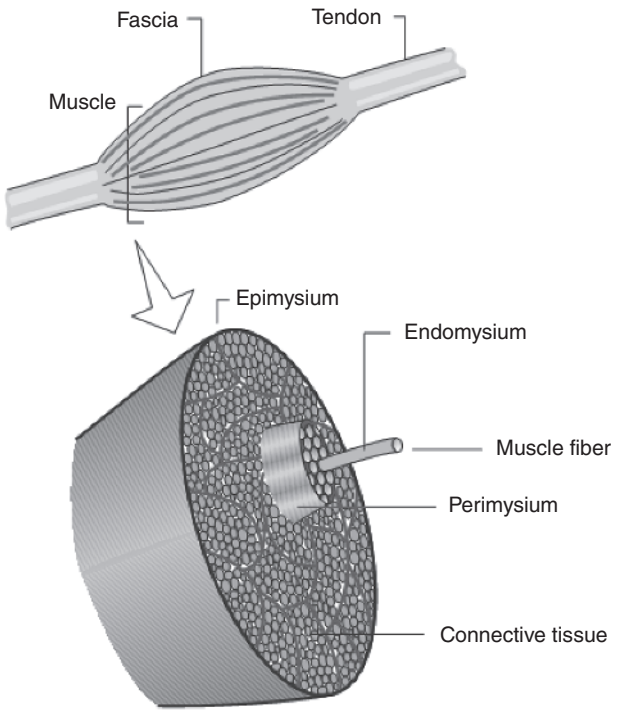

Figure 1.1.1 Skeletal muscle basic hierarchical structure. Adapted from Challis (2000)

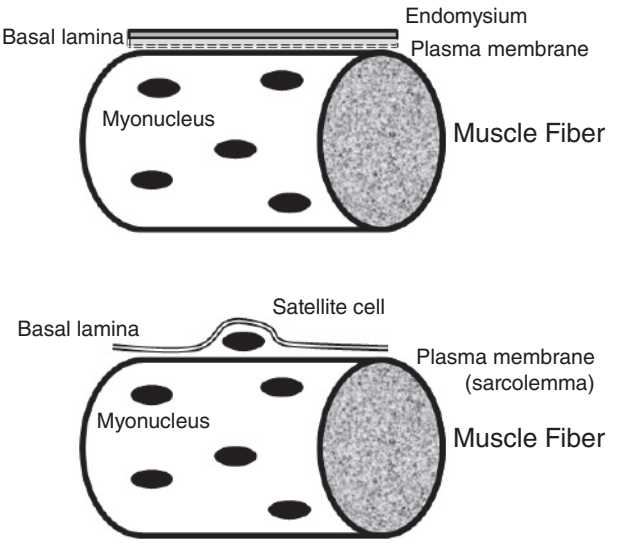

Figure 1.1.2 Illustration of a single multinucleated muscle fibre and satellite cell between the plasma membrane and the basal lamina

1.1.3.1 Sarcomere and myofilaments

A sarcomere is the smallest functional unit of a myofibre and is described as a structure limited by two Z disks or Z lines (Figure 1.1.3). Each sarcomere contains two types of myofilament: one thick filament called myosin and one thin filament called actin. The striated appearance of the skeletal muscle is the result of the positioning of myosin and actin filaments inside each sarcomere. A lighter area named the I band is alternated with a darker A band. The absence of filament overlap confers a lighter appearance to the I band, which contains only actin filaments, while overlap of myosin and actin gives a darker appearance to the A band. The Z line divides the I band in two equal halves; thus a sarcomere consists of one A band and two half-I bands, one at each side of the sarcomere. The middle of the A band contains the H zone, which is divided in two by the M line. As with the I band, there is no overlap between thick and thin filaments in the H zone. The M line comprises a number of structural proteins which are responsible for anchoring each myosin filament in the correct position at the centre of the sarcomere.

On average, a sarcomere that is between 2.0 and 2.25 μm long shows optimal overlap between myosin and actin filaments, providing ideal conditions for force production. At lengths shorter or larger than this optimum, force production is compromised (Figure 1.1.4).

The actin filament is formed by two intertwined strands (i.e. F-actin) of polymerized globular actin monomers (G-actin). This filament extends inward from each Z line toward the centre of the sarcomere. Attached to the actin filament are two regulatory proteins named troponin (Tn) and tropomyosin (Tm) which control the interaction between actin and myosin. Troponin is a protein complex positioned at regular intervals (every seven actin monomers) along the thin filament and plays a vital role in calcium ion (Ca^{++}) reception. This regulatory protein complex includes three components: troponin C (TnC), which binds Ca^{++}, troponin T (TnT), which binds tropomyosin, and troponin I (TnI), which is the inhibitory subunit. These subunits are in charge of moving tropomyosin away from the myosin binding site on the actin filament during the contraction process. Tropomyosin is distributed along the length of the actin filament in the groove formed by two F-actin strands and its main function is to inhibit the coupling between actin and myosin filaments from blocking active actin binding sites (Figure 1.1.5).

The thick filament is made mostly of myosin protein. A myosin molecule is composed of two heavy chains (MHCs) and two pairs of light chains (MLCs). It is the MHCs that determines muscle fibre phenotype. In mammalian muscles, the MHC component exists in four different isoforms (types I, IIA, IIB, and IIX), whereas the MLCs can be separated into two essential LCs and two regulatory LCs. Myosin heavy and light chains combine to fine tune the interaction between actin and myosin filaments during muscle contraction. A MHC is made of two distinct parts: a head (heavy meromyosin) and a tail (light meromyosin), in a form that may be compared to that of a golf club (Figure 1.1.6).

Approximately 300 myosin molecules are arranged tail-to-tail to constitute each thick filament (Brooks, Fahey and Baldwin, 2005). The myosin heads protrude from the filament;

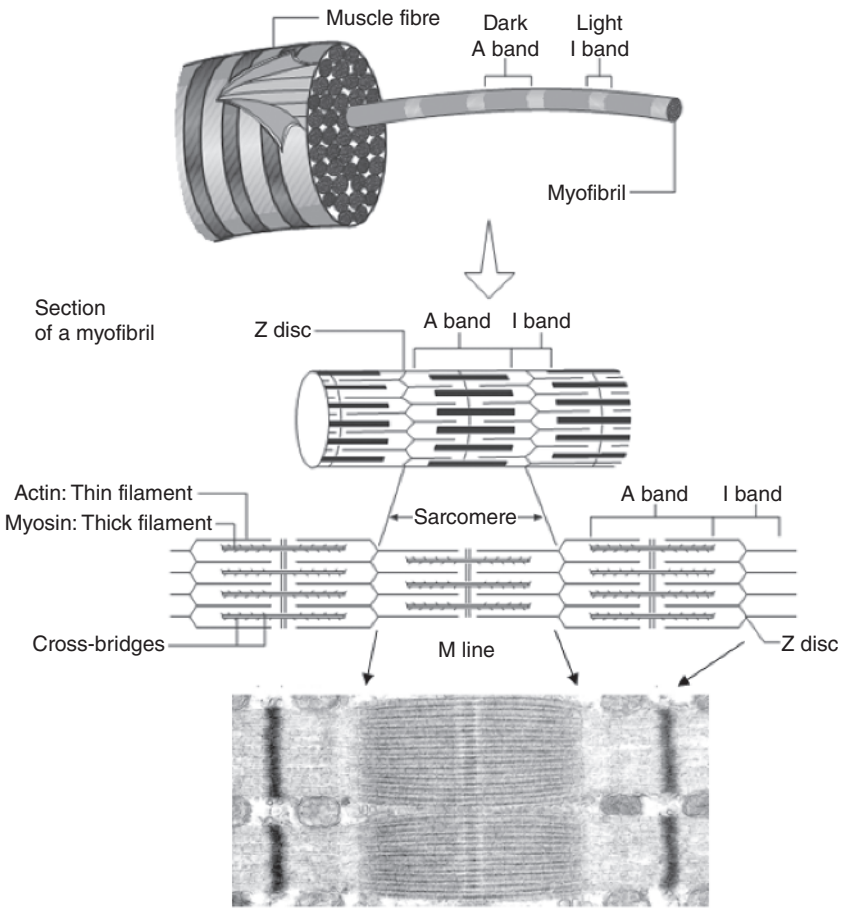

Figure 1.1.3 Representation of a muscle fibre and myofibril showing the structure of a sarcomere with actin and myosin filaments. Adapted from Challis (2000)

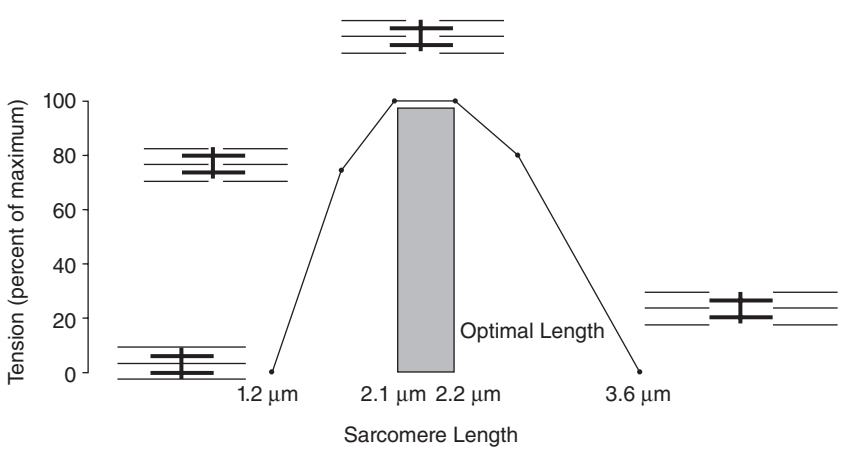

Figure 1.1.4 Skeletal muscle sarcomere length–tension relationship

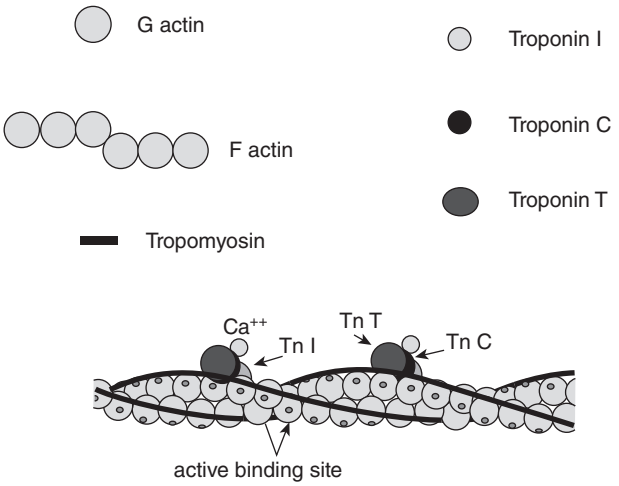

Figure 1.1.5 Schematic drawing of part of an actin filament showing the interaction with tropomyosin and troponin complex

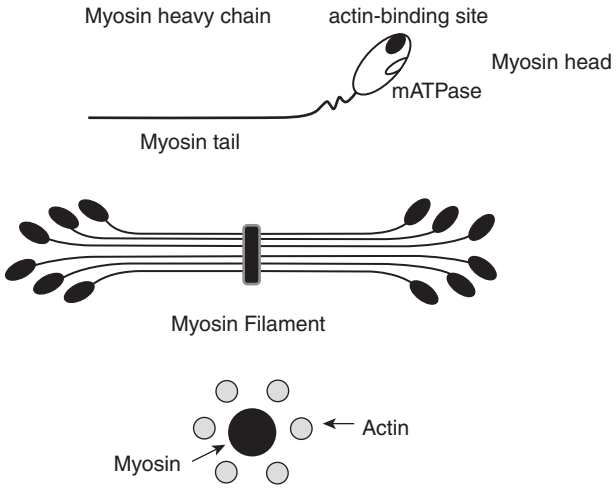

Figure 1.1.6 Schematic organization of a myosin filament, myosin heavy chain structure, and hexagonal lattice arrangement between myosin and actin filaments

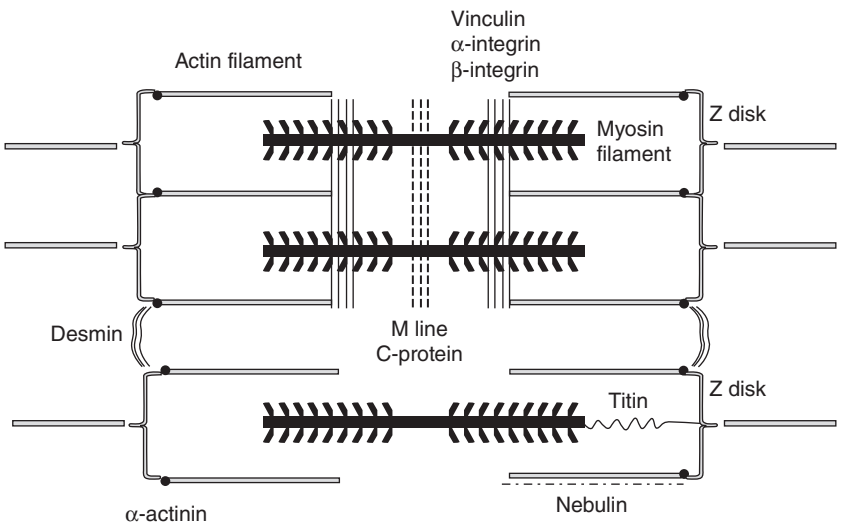

Figure 1.1.7 Illustration of the structural proteins in the sarcomere

each is arranged in a 60° rotation in relation to the preceding one, giving the myosin filament the appearance of a bottle brush. Each myosin head attaches directly to the actin filament and contains ATPase activity (see Section 1.1.5). Actin and myosin filaments are organized in a hexagonal lattice, which means that each myosin filament is surrounded by six actin filaments, providing a perfect match for interaction during contraction (Figure 1.1.6).

A large number of other proteins can be found in the interior of a muscle fibre and in sarcomeres; these constitute the so-called cytoskeleton. The cytoskeleton is an intracellular system composed of intermediate filaments; its main functions are to (1) provide structural integrity to the myofibre, (2) allow lateral force transmissions among adjacent sarcomeres, and (3) connect myofibrils to the cell's plasma membrane. The following proteins are involved in fulfilling these functions (Bloch and Gonzalez-Serratos, 2003; Hatze, 2002; Huijing, 1999; Monti *et al.*, 1999): vinculin, α- and β-integrin (responsible for the lateral force transmission within the fibre), dystrophin (links actin filaments with the dystroglycan and sarcoglycan complexes, which are associated with the sarcolemma and provide an extracellular connection to the basal lamina and the endomysium), α-actinin (attaches actin filaments to the Z disk), C protein (maintains the myosin

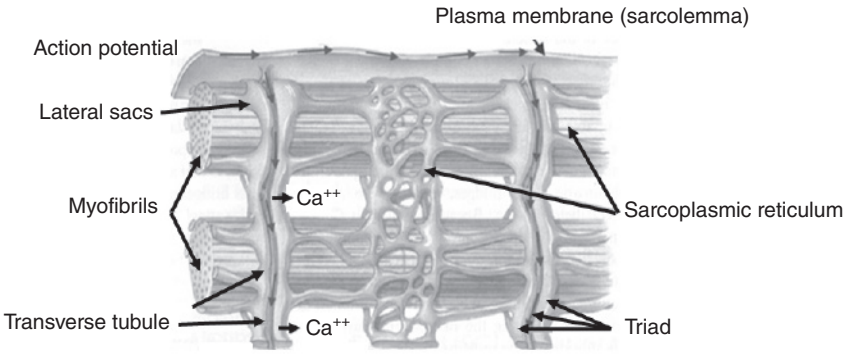

Figure 1.1.8 Representation of the transverse tubules (T tubules) and sarcoplasmic reticulum system

tails in a correct spatial arrangement), nebulin (works as a ruler, assisting the correct assembly of the actin filament), titin (contributes to secure the thick filaments to the Z lines), and desmin (links adjacent Z disks together). Some of these proteins are depicted in Figure 1.1.7.

1.1.3.2 Sarcoplasmic reticulum and transverse tubules

The sarcoplasmic reticulum (SR) of a myofibre is a specialized form of the endoplasmic reticulum found in most human body cells. Its main functions are (1) intracellular storage and (2) release and uptake of Ca^{++} associated with the regulation of muscle contraction. In fact, the release of Ca^{++} upon electrical stimulation of the muscle cell plays a major role in excitation–contraction coupling (E-C coupling; see Section 1.1.4). The SR can be divided into two parts: (1) the longitudinal SR and (2) the junctional SR (Rossi and Dirksen, 2006; Rossi *et al.*, 2008). The longitudinal SR, which is responsible for Ca^{++} storage and uptake, comprises numerous interconnected tubules, forming an intricate network of channels throughout the sarcoplasm and around the myofibrils. At specific cell regions, the ends of the longitudinal tubules fuse into single dilated sacs called terminal cisternae or lateral sacs. The junctional SR is found at the junction between the A and the I bands and represents the region responsible for Ca^{++} release (Figure 1.1.8).

The transverse tubules (T tubules) are organelles that carry the action potential (electrical stimulation) from the sarcolemma surface to the interior of the muscle fibre. Indeed, they are a continuation of the sarcolemma and run perpendicular to the fibre orientation axis, closely interacting with the SR. The association of a T tubule with two SR lateral sacs forms a structure called a triad which is located near each Z line of a sarcomere (Figure 1.1.8). This arrangement ensures synchronization between the depolarization of the sarcolemma and the release of Ca^{++} in the intracellular medium. It is the passage of an action potential down the T tubules that causes the release of intracellular Ca^{++} from the lateral sacs of the SR, causing muscle contraction; this is the mechanism referred to as E-C coupling (Rossi *et al.*, 2008).

1.1.4 CONTRACTION MECHANISM

1.1.4.1 Excitation–contraction (E-C) coupling

A muscle fibre has the ability to transform chemical energy into mechanical work through the cyclic interaction between actin and myosin filaments during contraction. The process starts with the arrival of an action potential and the release of Ca^{++} from the SR during the E-C coupling. An action potential is delivered to the muscle cell membrane by a motor neuron through the release of a neurotransmitter named acetylcholine (ACh). The release of ACh opens specific ion channels in the muscle plasma membrane, allowing sodium ions to diffuse from the extracellular medium into the cell, leading to the depolarization of the membrane. The depolarization wave spreads along the membrane and is carried to the cell's interior by the T tubules. As the action potential travels down a T tubule, calcium channels in the lateral sacs of the SR are opened, releasing Ca^{++} in the intracellular fluid. Calcium ions bind to troponin and, in the presence of ATP, start the process of skeletal muscle contraction (Figure 1.1.9).

1.1.4.2 Skeletal muscle contraction

Based on a three-state model for actin activation (McKillop and Geeves, 1993), the thin filament state is influenced by both Ca^{++} binding to troponin C (TnC) and myosin binding to actin. The position of tropomyosin (Tm) on actin generates a blocked, a closed, or an open state of actin filament activation. When intracellular Ca^{++} concentration is low, and thus Ca^{++} binding to TnC is low, the thin filament stays in a blocked state because Tm position does not allow actin–myosin interaction. However, the release of Ca^{++} by the SR and its binding to TnC changes the conformational shape of the troponin complex, shifting the actin filament from a blocked to a closed state. This transition allows a weak interaction of myosin heads with the actin filament, but during the closed state the weak interaction between myosin and actin does not produce force. Nevertheless, the weak interaction induces further movements in Tm, shifting the

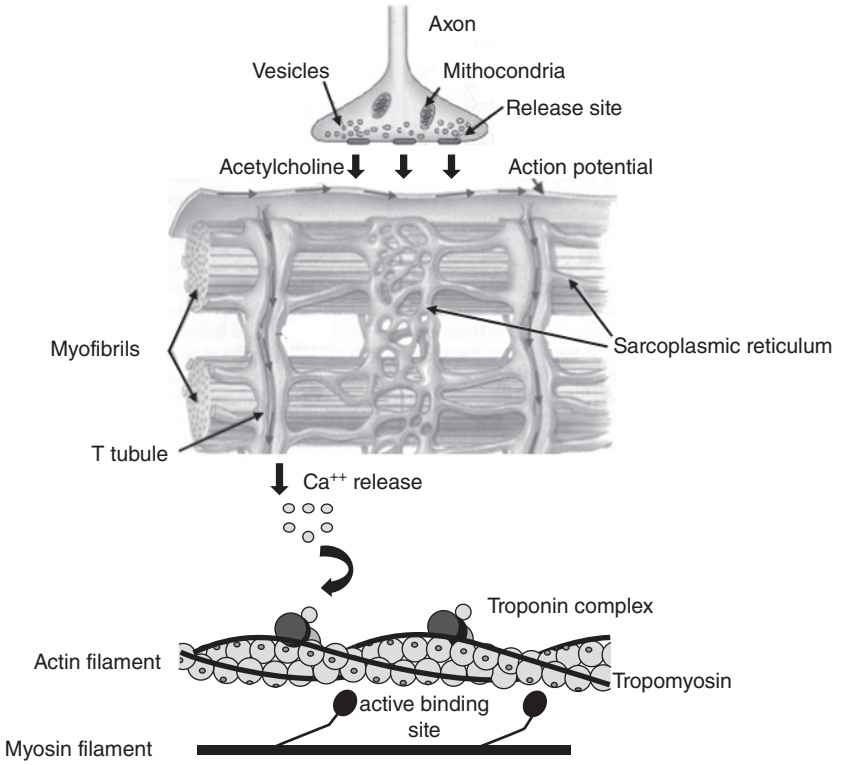

Figure 1.1.9 Excitation–contraction coupling and the sequence of events that will lead to skeletal muscle contraction

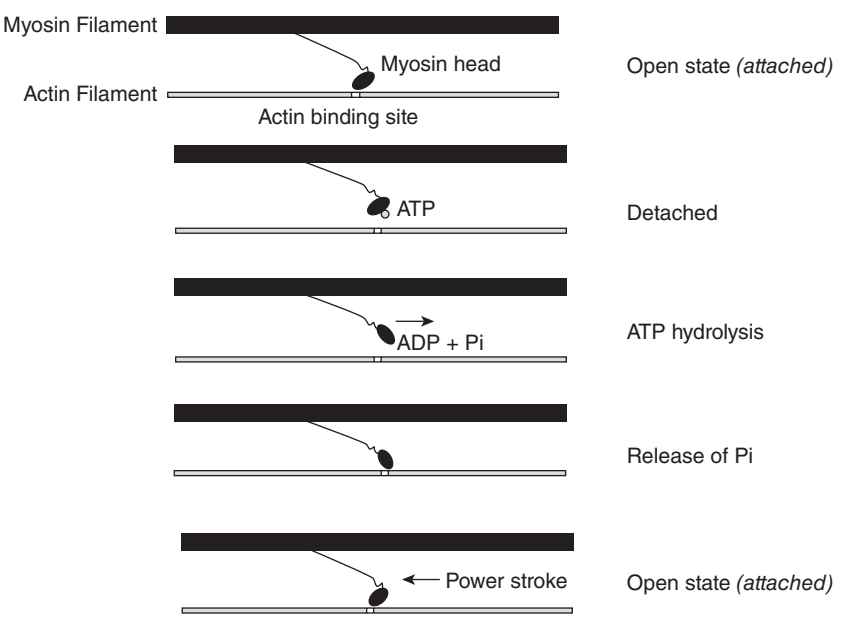

Figure 1.1.10 Cyclic process of muscle contraction

actin filament from the closed to the open state, resulting in a strong binding of myosin heads. In the open state, a high affinity between the myosin heads and the actin filament provides an opportunity to force production.

The formation of the acto-myosin complex permits the myosin head to hydrolyse a molecule of ATP and the free energy liberated is used to produce mechanical work (muscle contraction) during the cross-bridge power stroke (Vandenboom, 2004). Cross-bridges are projections from the myosin filament in the region of overlap with the actin filament. The release of ATP hydrolysis byproducts (Pi and ADP) induces structural changes in the acto-myosin complex that promote the cross-bridge cycle of attachment, force generation, and detachment. The force-generation phase is usually called the 'power stroke'. During this phase, actin and myosin filaments slide past each other and the thin filaments move toward the centre of the sarcomere, causing its shortening (Figure 1.1.10). Each cross-bridge power stroke produces a unitary force of 3–4 pico Newtons (1 pN = 10^{-12} N) over a working distance of 5–15 nanometres (1 nm = 10^{-9} m) against the actin filament (Finer, Simmons and Spudich, 1994). The resulting force and displacement per cross-bridge seem extremely small, but because billions of cross-bridges work at the same time, force output and muscle shortening can be large.

Interestingly, the myosin head retains high affinity for only one ligand (ATP or actin) at a time. Therefore, when an ATP molecule binds to the myosin head it reduces myosin affinity for actin and causes it to detach. After detachment, the myosin head rapidly hydrolyses the ATP and uses the free energy to reverse the structural changes that occurred during the power stroke, and then the system is ready to repeat the whole cycle (Figure 1.1.10). If ATP fails to rebind (or ADP release is inhibited), a 'rigour' cross-bridge is created, which eliminates the possibility of further force production. Thus, the ATP hydrolysis cycle is associated with the attachment and detachment of the myosin head from the actin filament (Gulick and Rayment, 1997). If the concentration of Ca^{++} returns to low levels, the muscle is relaxed by a reversal process that shifts the thin filament back toward the blocked state.

1.1.5 MUSCLE FIBRE TYPES

The skeletal muscle is composed of a heterogeneous mixture of different fibre types which have distinct molecular, metabolic, structural, and contractile characteristics, contributing to a range of functional properties. Skeletal muscle fibres also have an extraordinary ability to adapt and alter their phenotypic profile in response to a variety of environmental stimuli.

Muscle fibres defined as slow, type I, slow red or slow oxidative have been described as containing slow isoform contractile proteins, high volumes of mitochondria, high levels of myoglobin, high capillary density, and high oxidative enzyme capacity. Type IIA, fast red, fast IIA or fast oxidative fibres have been characterized as fast-contracting fibres with high oxidative capacity and moderate resistance to fatigue. Muscle fibres defined as type IIB, fast white, fast IIB (or IIx), or fast

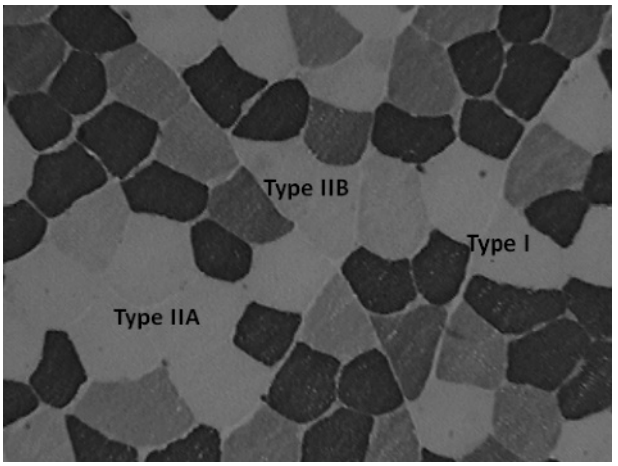

Figure 1.1.11 Photomicrograph showing three different muscle fibre types

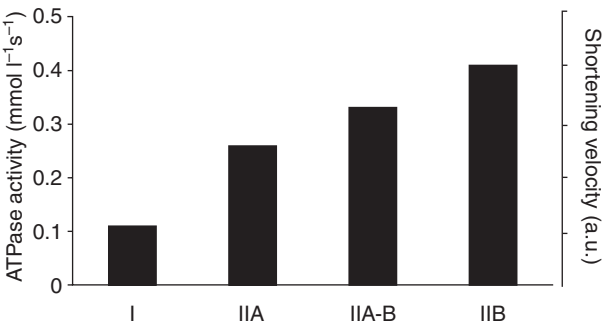

Figure 1.1.12 Representation of the relationship between skeletal muscle fibre type, mATPase activity, and muscle shortening velocity

glycolytic present low mitochondrial density, high glycolytic enzyme activity, high myofibrilar ATPase (mATPase) activity, and low resistance to fatigue (Figure 1.1.11).

Several methods, including mATPase histochemistry, immunohistochemistry, and electrophoretic analysis of myosin heavy chain (MHC) isoforms, have been used to identify myofibre types. The histochemical method is based on the differences in the pH sensitivity of mATPase activity (Brooke and Kaiser, 1970). Alkaline or acid assays are used to identify low or high mATPase activity. An ATPase is an enzyme that catalyses the hydrolysis (breakdown) of an ATP molecule. There is a strong correlation between mATPase activity and MHC isoform (Adams *et al.*, 1993; Fry, Allemeier and Staron, 1994; Staron, 1991; Staron *et al.*, 2000) because the ATPase is located at the heavy chain of the myosin molecule. This method has been used in combination with physiological measurements of contractile speed; in general the slowest fibres are classified as type I (lowest ATPase activity) and the fastest as type IIB (highest ATPase activity), with type IIA fibres expressing intermediate values (Figure 1.1.12). The explanation for these results is that

the velocity of the interaction between myosin and actin depends on the speed with which the myosin heads are able to hydrolyse ATP molecules (see Section 1.1.4).

Immunohistochemistry explores the reaction of a specific antibody against a target protein isoform. In this method, muscle fibre types are determined on the basis of their immunoreactivity to antibodies specific to MHC isoforms. An electrophoretic analysis is a fibre typing method in which an electrical field is applied to a gel matrix which separates MHC isoforms according to their molecular weight and size (MHCIIb is the largest and MHCI is the smallest). Because of the difference in size, MHC isoforms migrate at different rates through the gel. Immunohistochemical and gel electrophoresis staining procedures are applied in order to visualize and quantify MHC isoforms.

Independent of the method applied, the results have revealed the existence of 'pure' and 'hybrid' muscle fibre types (Pette, 2001). A pure fibre type contains only one MHC isoform, whereas a hybrid fibre expresses two or more MHC isoforms. Thus, in mammalian skeletal muscles, four pure fibre types can be found: (1) slow type I (MHCIβ), (2) fast type IIA (MHCIIa), (3) fast type IID (MHCIId), and (4) fast type IIB (MHCIIb) (sometimes called fast type IIX fibres) (Pette and Staron, 2000). Actually, type IIb MHC isoform is more frequently found in rodent muscles, while in humans type IIx is more common (Smerdu *et al.*, 1994).

Combinations of these major MHC isoforms occur in hybrid fibres, which are classified according to their predominant isoform. Therefore, the following hybrid fibre types can be distinguished: type I/IIA, also termed IC (MHCIβ > MHCIIa); type IIA/I, also termed IIC (MHCIIa > MHCIβ); type IIAD (MHCIIa > MHCIId); type IIDA (MHCIId > MHCIIa); type IIDB (MHCIId > MHCIIb); and type IIBD (MHCIIb > MHCIId) (Pette, 2001). All these different combinations of MHCs contribute to generating the continuum of muscle fibre types represented below (Pette and Staron, 2000):

TypeI ↔ TypeIC ↔ TypeIIC ↔ **TypeIIA** ↔ TypeIIAD ↔ TypeIIDA ↔ **TypeIID** ↔ TypeIIDB ↔ TypeIIBD ↔ **TypeIIB**

Despite the fact that chronic physical exercise, involving either endurance or strength training, appears to induce transitions in the muscle fibre type continuum, MHC isoform changes are limited to the fast fibre subtypes, shifting from type IIB/D to type IIA fibres (Gillies *et al.*, 2006; Holm *et al.*, 2008; Putman *et al.*, 2004).The reverse transition, from type IIA to type IIB/D, occurs after a period of detraining (Andersen and Aagaard, 2000; Andersen *et al.*, 2005). However, it is still controversial whether training within physiological parameters can induce transitions between slow and fast myosin isoforms (Aagaard and Thorstensson, 2003). The amount of hybrid fibre increases in transforming muscles because the coexistence of different MHC isoforms in a myofibre leads it to adapt its phenotype in order to meet specific functional demands.

How is muscle fibre type defined? It appears that even in foetal muscle different types of myoblast exist and thus it is likely that myofibres have already begun their differentiation into different types by this stage (Kjaer *et al.*, 2003); innervation, mechanical loading or unloading, hormone profile, and ageing all play a major role in phenotype alteration.

The importance of innervation in the determination of specific myofibre types was demonstrated in a classic experiment of cross-reinnervation (for review see Pette and Vrbova, 1999): fast muscle phenotype became slow once reinnervated by a slow nerve, while a slow muscle became fast when reinnervated by a fast nerve. Nevertheless, motor nerves are not initially required for the differentiation of fast and slow muscle fibres, although innervation is later essential for muscle growth and survival. Motor innervation is also involved in fibre type differentiation during foetal development.

Curiously, unloaded muscles show a tendency to convert slow fibres to fast ones (Gallagher *et al.*, 2005; Trappe *et al.*, 2004, 2009). This shift in fibre type profile was observed in studies involving microgravity conditions (spaceflight or bed-rest models). It appears that slow MHC isoforms are more sensitive to the lack of physical activity than fast isoforms (Caiozzo *et al.*, 1996, 2009; Edgerton *et al.*, 1995).

A hormonal effect on muscle fibre phenotypes is markedly observed with thyroid hormones. In skeletal muscles, thyroid hormones reduce MHCI gene transcription, while they stimulate transcription of MHCIIx and MHCIIb. The effects on the transcription of the MHCIIa gene are muscle-specific: transcription is activated in slow muscles such as soleus and repressed in fast muscles such as diaphragm (Baldwin and Haddad, 2001; DeNardi *et al.*, 1993). Thus, in general, reduced levels of thyroid hormone cause fast-to-slow shifts in MHC isoform expression, whereas high levels of thyroid hormone cause slow-to-fast shifts (Canepari *et al.*, 1998; Li *et al.*, 1996; Vadászová *et al.*, 2004).

In addition to muscle atrophy and a decrease in strength, ageing may cause fast-to-slow fibre type transitions (Canepari *et al.*, 2009; Korhonen *et al.*, 2006). Degenerative processes in the central nervous system (CNS) and/or peripheral nervous system (PNS), causing denervation (selective loss of fast α-motor neurons) and reinnervation (with slow α-motor neurons), physical inactivity, and altered thyroid hormone levels, may contribute to the observed atrophy and potential loss of fast muscle fibres in elderly people.

1.1.6 MUSCLE ARCHITECTURE

Skeletal muscle architecture is defined as the arrangement of myofibres within a muscle relative to its axis of force generation (Lieber and Fridén, 2000). Skeletal muscles present a variety of fasciculi arrangements but they can be described mostly as fusiforms or pennate muscles. A fusiform muscle has fibres organized in parallel to its force-generating axis and is described as having a parallel or longitudinal architecture. A pennate muscle has fibres arranged at an oblique angle to its force-generating axis (Figure 1.1.13).

Muscle fibre arrangement has a functional significance and the effect of muscle design on force production and contraction velocity is remarkable. In a fusiform muscle, the myofibres cause force production to occur directly at the tendon; the parallel arrangement allows fast muscle shortening. In a pennate

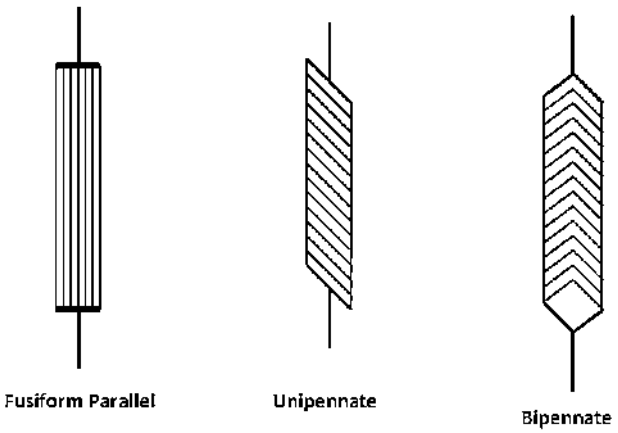

Figure 1.1.13 Muscle architecture: three different arrangements of muscle fibres (fusiform, unipennate, and bipennate). The angle at resting length in mammalian muscles varies from 0° to 30°

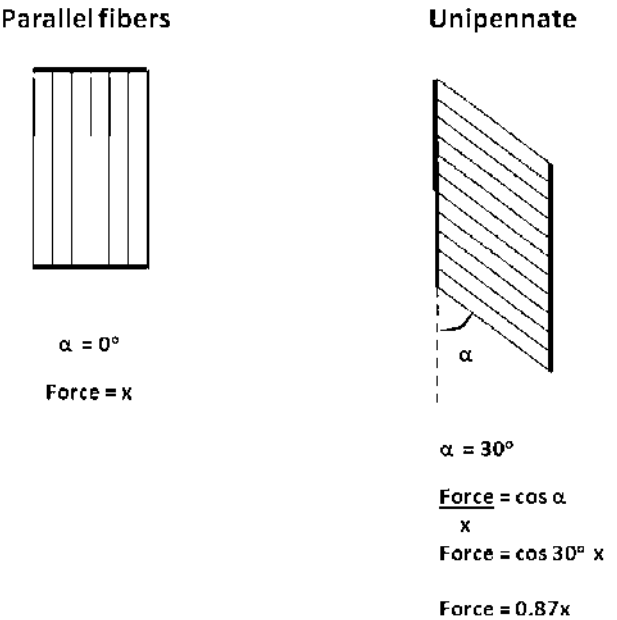

Figure 1.1.14 Representation of the effect of muscle fibre arrangement. Fibres orientated parallel to the axis of force generation transmit all of their force to the tendon. Fibres orientated at a 30° angle relative to the force-generation axis transmit part of their force to the tendon, proportional to the angle cosine. Adapted from Lieber (1992)

muscle, fascicule angle affects force transmission and decreases shortening velocity. Because fibres are orientated at an angle relative to the axis of force generation, not all fibre tensile force is transmitted to the tendons and only a component of fibre force production is actually transmitted along the muscle axis, in proportion to the pennation angle cosine (Figure 1.1.14). It seems that pennate arrangement is detrimental to muscle strength performance as it results in a loss of force compared with a muscle of the same mass and fibre length but zero pennation angle. However, a muscle with pennate fibres is able to generate great amounts of force. In fact, high-intensity strength training causes increases in pennation angle (Aagaard *et al.*, 2001; Kawakami, Abe and Fukunaga, 1993; Kawakami *et al.*, 1995; Reeves *et al.*, 2009; Seynnes, de Boer and Narici, 2007) which enhance the muscle's ability to pack more sarcomeres and myofibres, creating a large physiological cross-sectional area (PCSA). A PCSA is measured perpendicular to the fibre orientation, whereas an anatomical cross-sectional area (ACSA) is measured perpendicular to the muscle orientation. A large PCSA positively affects the force-generating capacity of the muscle, compensating for the loss in force transmission due to increases in pennation angle (Lieber and Fridén, 2000).

Two other important parameters in architectural analysis are muscle length and fibre length. Muscle velocity is proportional to muscle/fibre length. Muscles with similar PCSAs and pennation angles but different fibre lengths have different velocity outputs. The muscle with the longest fibres presents greater contraction velocity, while shorter muscles are more suitable for force production with low velocity. Thus, antigravity short extensor muscles are designed more for force production, while longer flexors are for long excursions with higher velocity. The soleus muscle, with its high PCSA and short fibre length, suitable for generating high force with small excursion, is a good example of an antigravity postural muscle, while the biceps femoris is an example of a long flexor muscle suitable for generating high velocity with long excursion.

1.1.7 HYPERTROPHY AND HYPERPLASIA

A good example of skeletal muscle's ability to adapt to environmental stimuli is the hypertrophy that occurs after a period of strength training. Hypertrophy can be defined as the increase in muscle fibre size and/or muscle mass due to an accumulation of contractile and noncontractile proteins inside the cell (Figure 1.1.15). Increased rate of protein synthesis, decreased rate of protein breakdown, or a combination of both of these factors, is responsible for muscle hypertrophy (Rennie *et al.*, 2004). Most of us are in a state of equilibrium between muscle protein synthesis and protein degradation; thus muscle mass remains constant. Muscle size and muscle mass can also be enlarged by way of hyperplasia, which is an increase in the number of myofibres. However, the suggestion that new muscle fibres may form in human adults as a result of strength training is still highly controversial (Kadi, 2000). Hyperplasia has been demonstrated following strength training in some animal models (Antonio and Gonyea, 1993; 1994; Tamaki *et al.*, 1997) but the evidence in human subjects is unclear (Kelley, 1996; McCall *et al.*, 1996).

Hypertrophy-orientated strength training affects all muscle fibre types, however type II fast fibres have usually shown a more pronounced response than type I slow fibres (Aagaard

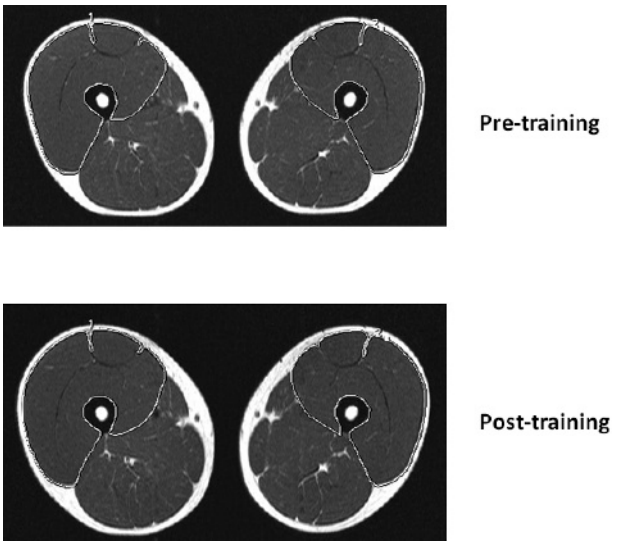

Figure 1.1.15 Magnetic resonance image of the quadriceps femoris before and after a period of strength training

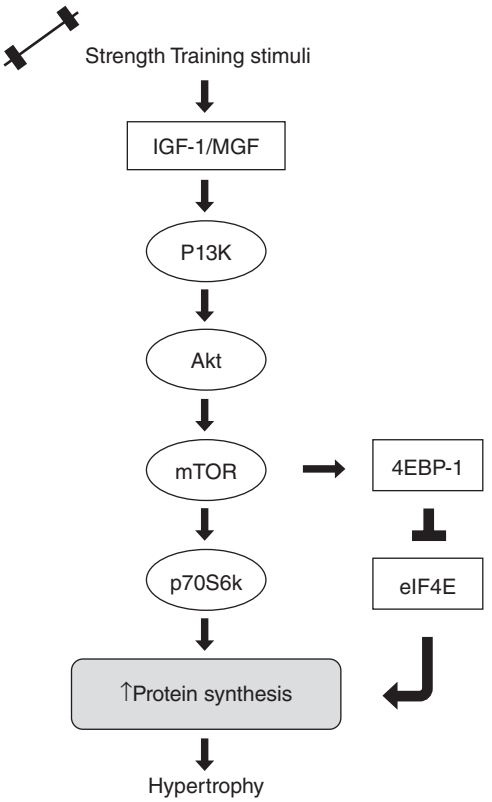

Figure 1.1.16 Schematic illustration of the effect of strength training stimuli on activation of the hypertrophy pathway

et al., 2001; Cribb and Hayes, 2006; Verdijk *et al.*, 2009). It appears that type II fibres possess a greater adaptive capacity for hypertrophy than type I fibres. This is interesting because it has been demonstrated that muscle protein synthesis does not differ between fibre types after a bout of strength training exercise (Mittendorfer *et al.*, 2005). Similarly, satellite cells, which are important contributors to muscle hypertrophy (see Section 1.1.8), are equally distributed in human vastus lateralis type I and type II fibres (Kadi, Charifi and Henriksson, 2006).

The question of how mechanical signals provided by strength training are translated into increased muscle protein synthesis and hypertrophy has not been fully answered. It is beyond the scope of this chapter to deeply explain the possible mechanism and intracellular pathways involved in muscle hypertrophy (for more details see Spangenburg, 2009; Zanchi and Lancha, 2008). In brief, high tension applied over skeletal muscles during strength training stimulates the release of growth factors such as insulin-like growth factor 1 (IGF-1). It has been shown that this hormone is involved in muscle hypertrophy through autocrine and/or paracrine mechanisms (Barton-Davis, Shoturma and Sweeney, 1999). IGF-1 is a potent activator of the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signalling pathway, which is a key regulator in protein synthesis. Activation of Akt is mediated by the IGF-1/phosphatidylinositol-3 kinase (PI3K) pathway. Once activated, Akt activates mTOR, which in turn activates 70 kDa ribosomal S6 protein kinase (p70S6k), a positive regulator of protein translation (Baar and Esser, 1999). The degree of activation of p70S6k is closely associated with the subsequent protein synthesis and muscle growth. mTOR also inhibits the activity of 4E binding protein 1 (4E-BP1), a negative regulator of the protein-initiation factor eIF-4E, which is involved in translation initiation and like p70S6k contributes to enhanced protein synthesis (Koopman *et al.*, 2006). Any alteration in mTOR activation will result in changes in p70s6k activation and 4EBP-1 inactivation, ultimately affecting the initiation of protein synthesis and causing increases in muscle size and mass (Figure 1.1.16). It appears that muscle tension per se may also stimulate skeletal muscle growth through a mechanism called mechano-transduction; the regulation of the Akt/mTOR signalling pathway in response to mechanical stimuli is still not well understood however (Rennie *et al.*, 2004).

1.1.8 SATELLITE CELLS

Adult skeletal muscle contains a cell population with stem cell-like properties called satellite cells (SCs) (Hawke, 2005). These are located at the periphery of myofibres, between the basal lamina and the sarcolemma (Figure 1.1.2) (Vierck *et al.*, 2000; Zammit, 2008). Skeletal muscle SCs are undifferentiated quiescent myogenic precursors that display self- renewal properties (Huard, Cao and Qu-Petersen, 2003), which means that they can generate daughter cells which can become new SCs (Kadi

et al., 2004; Zammit and Beauchamp, 2001). They serve as reserve cells and are recruited when myofibre growth and/or regeneration after injury is needed. In response to signals associated with muscle damage, mechanical loading, and exercise, SCs leave the quiescent state, become activated, and reenter the cell cycle (Hawke and Garry, 2001; Tidball, 2005). After activation, these cells proliferate and migrate to the site of injury to repair or replace damaged myofibres by fusing together to create a myotube or by fusing to existing myofibres (Hawke, 2005; Machida and Booth, 2004).

It appears that the fusion of SCs to existing myofibres is also critical for increases in fibre cross-sectional area. This physiological event takes into consideration the concept of the myonuclear domain or DNA unit, which suggests that each myonucleus manages the production of mRNA and protein synthesis for a specific volume of sarcoplasm (Adams, 2002; Kadi and Thornell, 2000; Petrella *et al.*, 2008). It has been proposed that there may be a limit on the amount of expansion a myonuclear domain can undergo during hypertrophy (i.e. a domain ceiling size) (Kadi *et al.*, 2004). A limit indicates that an expansion of the myonuclear domain toward a threshold >2000 μm^2/nucleus (Petrella *et al.*, 2006), or between 17 and 25% of the fibre's initial size (Kadi *et al.*, 2004), may put each myonucleus under greater strain, thus increasing the demand for new myonuclei to make continued growth possible (Petrella *et al.*, 2008).

This implies that increases in muscle fibre size (i.e. hypertrophy) must be associated with a proportional increase in myonucleus number. However, muscle fibres are permanently differentiated, and therefore incapable of producing additional myonuclei through mitosis (Hawke and Garry, 2001; Machida and Booth, 2004). Nevertheless, it has been shown that myonucleus number increases during skeletal muscle hypertrophy, in order to maintain the cytoplasm-to-myonucleus ratio (Allen *et al.*, 1995; Petrella *et al.*, 2006), and the only alternative source of additional myonuclei is the pool of SCs (Kadi, 2000; Rosenblatt and Parry, 1992). In adult skeletal muscles, it has been observed that satellite cell-derived myonuclei are incorporated into muscle fibres during hypertrophy (Kadi and Thornell, 2000). Following the initial increase in muscle fibre size that occurs via increased mRNA activity and protein accretion, the incorporation of additional myonuclei in muscle fibres represents an important mechanism for sustaining muscle fibre enlargement (Petrella *et al.*, 2006). Incorporated satellite cell-derived myonuclei are no longer capable of dividing, but they can produce muscle-specific proteins that increase myofibre size (Allen, Roy and Edgerton, 1999), resulting in hypertrophy.

The mechanisms by which skeletal muscle SCs are activated and incorporated into growing myofibres are still unclear but it has been suggested that they are modulated by cytokines and autocrine/paracrine growth factors (Hawke and Garry, 2001; Petrella *et al.*, 2008). For example, strength exercises induce damage to the sarcolemma, connective tissue, and muscle fibre structural and contractile proteins, initiating an immune response which then attracts macrophages to the damaged area. Macrophages secrete a number of cytokines, which regulate the SCs pool. In order to regenerate the damaged myofibres, SCs differentiate and fuse together to generate a myotube, which then fuses to the damaged muscle fibre, repairing the injury.

Despite the differences between skeletal muscle regeneration and hypertrophy, both processes share similarities regarding SCs activation, proliferation, and differentiation. It is believed that muscle-loading conditions (i.e. strength training) stimulate the release of growth factors (IGF-1 and MGF), which affects SC activation, proliferation and differentiation (Adams and Haddad, 1996; Bamman *et al.*, 2007; Vierck *et al.*, 2000). Insulin-like growth factor-1 (IGF-1) and its isoform mechano-growth factor (MGF) are potent endocrine and skeletal muscle autocrine/paracrine growth factors. IGF-1 is upregulated in response to hypertrophic signals in skeletal muscle and promotes activation, proliferation and fusion of the SCs. During skeletal muscle hypertrophy, SCs fuse to the existing myofibres, essentially donating their nuclei, whereas in regeneration from more extensive muscle damage SCs fuse together to generate a new myotube, which repairs damaged fibres (Hawke, 2005).

The ageing process decreases the number of SCs and negatively affects their proliferative capacity; these two factors may be related to the atrophy and poor muscle regeneration described in some elderly individuals (Crameri *et al.*, 2004; Kadi *et al.*, 2004).

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