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# Regeneration of Skeletal Muscle Fibers and Regulation of Myosatellitocytes Metabolism

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**Abstract**—Skeletal muscles are heterogeneous tissue containing different types of muscle fibers. Their distribution depends on heredity, type of exercise, sex, age, and muscle type. In addition, stem cells (myosatellitocytes) are found in large amounts in the muscle tissue. Myosatellitocytes are the main material for regeneration of microtears of muscle fibers always occuring during intensive physical exercises. Myosatellitocytes are capable of long-term storage in an inactive "dormant" state, but they can be rapidly activated to provide an efficient repair of damaged muscle fibers. The metabolism of myosatellitocytes and myoblasts and their migration into the damaged area are regulated by a complex system of cytokines and transcription factors, the activity of which depends on many factors. Microtears initiating the development of the inflammatory process and activation of myosatellitocytes is a determining factor. The study into molecular mechanisms of the relationship between inflammatory processes in muscle tissue and changes in myosatellitocyte metabolism is of fundamental importance and is necessary for the selection of efficient methods for muscle tissue recovery.

**Keywords:** myosatellitocytes, nucleotide polymorphisms, transcription factors, skeletal muscles, regeneration
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## TYPES OF MUSCLE FIBERS AND THEIR DISTRIBUTION IN SKELETAL MUSCLES

Myoblasts localized in certain areas of the embryos are developed into human skeletal muscles. Most of them give rise to the development of myosymplasts (fused myocytes), where myofibrils are subsequently formed. The rest differentiate into myosatellitocytes, muscle stem cells (mitotic $G_1$ myoblasts).

Human skeletal muscle is a very heterogeneous tissue composed of muscle fibers, connective tissue skeleton, vessels and nerves. A muscle fiber consisting of myosymplast and myosatellitocytes covered by a common basal membrane is a basic structural unit of striated muscle tissue. Muscle fibers can be divided into three main types: I, IIa, and IIx, corresponding to the type IIb in animals. Type I includes slow contractile but fatigue-resistant muscle fibers. Type IIa are fast contractile and less fatigue-resistant. Type IIx are the most fatigued fibers; however, they provide the highest, short-term muscle power. In general, it is considered that difference in the value of ATPase activity of myosin is the main differences between type I and type II fibers (Suwa et al., 1996; Scott et al., 2001).

Data on the activity of catabolic enzymes and isoforms of heavy chains of myosin are also used for the classification of muscle fibers; however, this led to significant contradictions in a number of cases; therefore, the majority of authors adhere to the main classification (types I, IIa, and IIx) (Scott et al., 2001; Fuku et al., 2019).

Red muscle fibers (type I) are able to oxidize the final product of anaerobic glycolysis (lactate), which (during intensive physical activity) is actively produced and exported by type II fibers. There is a direct correlation between the oxidative power of red muscle fibers and the activity of membrane lactate transporter MCT1 (monocarboxylate transporters—MCTs), which provides active absorption of lactate. At the same time, the presence of another transporter (MCT4), on the contrary, provides the export of lactate from the fiber to the outside and into the blood (Halestrap and Wilson, 2012; Bisetto et al., 2019).

The content of fibers of a certain type in human muscles varies widely. Type I fibers can account for 15–85% of the total number; IIa and IIx, 5–77 and 0–44%, respectively (Fuku et al., 2019). Since the skeletal muscles constitute 30–45% of the body weight, and their metabolism consumes about a quarter of the body's energy production, the studies of the factors affecting the content of fibers of a certain type and the

mechanisms of their energy supply are extremely important (Gerrits et al., 2010; Hardie et al., 2012; Sybil et al. 2015; Kutseryb et al., 2019).

Heredity is one of the main factors affecting the content of fibers of a certain type in human muscles. The results of human genome sequencing (including highly qualified athletes) allowed for establishing a number of alleles of the genes that affect the development of skeletal muscles and the specialization of fibers, in particular.

The nucleotide substitution (C → T) in the ACTN3 gene leads to the synthesis of truncated α-actinin, which serves to attach actin filaments to the Z-disk. It was found that the muscles of males with C/C or C/T genotypes contain more white powerful type IIx fibers than the muscles of males with T/T genotypes, which is significantly less common in highly qualified sprinters and representatives of other kinds of sports, where high power is needed (Ahmetov et al., 2011).

Angiotensin-converting enzyme (ACE), which plays a key role in the regulation of the tone (lumen) of blood vessels, is another example. It was established that male carriers of the D allele of this gene in Japan have a higher content of type I fibers (Kumagai et al., 2018).

Nucleotide polymorphisms in other genes (HIFIA, KDR, AGTR2) were also described in a number of works as affecting the content of type I fibers in males from certain populations. It should be noted that the list of genes that can theoretically influence the content of certain muscle fibers is quite extensive. However, the proof of their role and the establishment of the mechanism of action require further studies and taking into account the influence of sex and age peculiarities on the muscle structure (Haizlip et al., 2015; Fuku et al., 2019).

Disagreements in current sports regulations for males and females can indicate that the female organism is better adapted for long-term aerobic physical exercise. This is confirmed by many studies indicating a relatively higher content of slow type I fibers and a decrease in IIa and IIx in female muscles. Thus, a balance of sex hormones also affects the ratio of different types of fibers in the muscles (Haizlip et al., 2015; Kumagai et al., 2018).

Age is another factor, which significantly affects the content of certain fibers in the muscle. A decrease in the content of type I fibers is observed in the period 5–25 years; at the same time, the cross-sectional area of all muscle fibers increases significantly. As a consequence, peak muscle strength and mass occurs in the period between 20 and 30 years. A significant decrease in the content of type II fibers was detected during the long-term observation of older males who are still physically active (Kumagai et al., 2018). The results of other studies indicated that the proportion of type II fibers in *m. biceps brachii* does not change, while their thickness (cross-sectional area) decreases significantly with age. It is possible that this contradiction is explained by the fact that the described changes depend both on age, on the muscle selected for the study, and on the type of physical activity (Klein et al., 2003; Hendrickse et al., 2021). A decrease in the total amount of muscle fibers by 8–24% with age and an increase in the amount of noninnervated fibers was also described. In many cases, these changes are accompanied by an increase in the amount of intramuscular adipose tissue, which worsens the physical and mechanical properties of muscles (Wilkinson et al., 2018).

At the same time, certain physical exercises contribute to a physiological increase in the size and mass of skeletal muscles (hypertrophy) regardless of age. Interval training (performing exercises with a significant load with a maximum of 6–12 repeats followed by a short rest period) are the most efficient trigger of repair processes and muscle hypertrophy (Vierck et al., 2000; Schoenfeld, 2010).

Depending on the load intensity, exercise rate, number of repeats, and duration of rest, such training can cause myofibrillar and/or sarcoplasmic hypertrophy. An increase in the sarcoplasm volume (sarcoplasmic hypertrophy) can be accompanied by a significant increase in the muscle mass without a significant increase in their strength capabilities. With an increase in the number of myofibrils (myofibrillar hypertrophy), a total increase in the muscle mass is less pronounced than with sarcoplasmic hypertrophy (Vierck et al., 2000; Schoenfeld, 2010).

## DAMAGE TO MUSCLE TISSUE: INFLAMMATORY PROCESSES AND PAIN SENSATION

Intense muscle contraction leads to a rupture of individual myocytes and development of local inflammation. On the one hand, inflammation refers to the most common typical pathological processes in the organism; on the other hand, it is an important adaptive defense reaction, which is based on a combination of nervous, humoral, and effector mechanisms initiating the repair processes in the muscle tissue. The pain that occurs during the inflammation is one of the essential components of the organism's defense reaction.

The inflammatory process has a clear staging and includes three main stages: damage to cells or tissues (alteration) microcirculation disorders with exudation and migration of blood cells, and healing (proliferation and differentiation of the cells in the affected area and restoration of the integrity of damaged tissue).

Tissue damage initiates the initial phase of inflammation in which the formation and release of inflammatory mediators that regulate this process occurs. Violation of the functioning of mitochondria (which is almost always observed with a damage to myosymplasts) leads to a decrease in ATP synthesis, activation

of glycolysis, and is accompanied by nonenzymatic oxidation of polyunsaturated fatty acids (particularly, arachidonic) with the formation of lipid hydroperoxides (Dong et al., 2006; Kumar et al., 2012; Nathan and Cunningham-Bussel, 2013). Specifically these hydroperoxides are low molecular weight effectors (chemoattractants) that cause migration of leukocytes and their infiltration into the inflammation zone. An increase in local concentration of lactate (a consequence of the activation of glycolysis) leads to the development of local acidosis and activation of hydrolytic enzymes of lysosomes, which enhances the processes of cell damage. In addition, damage to the muscle cells leads to a release of $K^+$ ions from the cells and entry of $Na^+$ and $Ca^{2+}$ ions into them, which leads to cell swelling and activation of membrane phospholipases and cytosolic proteinases (Dong et al., 2006). As a consequence, the activation (by phosphorylation) of membrane-associated phospholipase $A_2$ (hydrolyzing phospholipids and releasing arachidonic acid from them) occurs (Ricciotti and FitzGerald, 2011). Arachidonic acid (AA) (5,8,11,14-eicosatetraenoic acid) is one of the key low molecular weight precursors of proinflammatory mediators (Fig. 1).

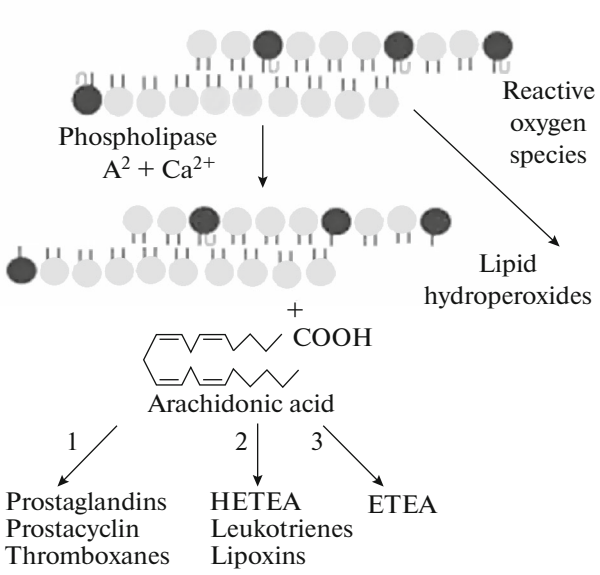


**Fig 1.** Scheme of formation of proinflammatory metabolites in muscle cell damage. (1) Cyclooxygenases COX 1 and COX 2; (2) lipoxygenases; (3) cytP450/epoxygenase; HETEA, hydroxyeicosatetraenoic acids; EETEA, epoxyeicosatetraenoic acids.

Thus, the synthesis of proinflammatory mediators is normally limited by three factors: absence of lipid hydroperoxides, inaccessibility of ether bonds of phospholipids for phospholipase $A_2$ (which, in addition, is not activated), and inaccessibility of arachidonic acid for cytosolic oxygenases. Such triple control mechanism normally prevents the inflammatory processes and provides their efficient launch when needed. In case of violation of any component of this triple mechanism, the inflammatory process develops.

After enzymatic cleavage from phospholipids, arachidonic acid can be enzymatically oxidized (Needleman et al., 1986; Panigrahy et al., 2010) in three main ways: cyclooxygenase, which leads to the synthesis of prostaglandins, prostacyclin, and thromboxanes; lipoxygenase (catalyzed by lipoxygenases of eosinophils migrated from the bloodstream to the inflammation zone) resulting in the formation of leukotrienes and lipoxins; cytochrome (monooxygenase), which leads to the formation of epoxyeicosatetraenoic acids (Kantarci and Van Dyke, 2003; Radmark et al., 2015).

As is known, prostaglandins (PG), among which prostacyclin and prostaglandins PGE2 and PGF2α are the most active, are the main low molecular weight mediators of inflammation. Prostaglandins have both local and systemic effects, while prostaglandin receptors are contained in the cytoplasmic membranes of the vast majority of human organism cells (Ricciotti and Fitzgerald, 2011).

The emergence of inflammatory mediators at the place of skeletal muscle injury and increased local concentration of neurotransmitters leads to the stimulation of type C muscle nociceptors (pain receptors of specialized nerve fibers). Potassium and hydrogen ions (acidification), ATP, bradykinins, etc. are direct nociceptor stimuli. With a constant activation of chemical nociceptors (during inflammation, tissue damage), their sensitivity gradually increases, resulting in an increase in pain sensations. This is caused by an increase in the content of histamine, prostaglandins, and kinins in the tissues (modulating the sensitivity of nociceptive chemoreceptors) as well as by an increase in the production of nerve growth factor (effects of TNFα, IL-1, basophils, eosinophils) and, respectively, an increase in the amount of receptors for unmyelinated C fibers (the phenomenon of increased sensitivity to pain stimuli (hyperalgesia) occurs) (Lamont et al., 2000). The pain causes vasoconstriction, an increase in the heart rate, and increased secretion of renin, angiotensin, aldosterone, catecholamines, glucagon, cortisol along with a decrease in the production of insulin and testosterone (Wright and Woodson, 1990; Lamont et al., 2000). In turn, this causes a series of changes in the metabolism of the entire tissue (and the organism) that activate repair processes at the tissue level.

## STEM CELLS OF MUSCLE TISSUE AND MUSCLE REGENERATION

Simultaneously with the inflammation in damaged muscle tissue, dormant stem cells are activated, proliferate, differentiate, and migrate to the damaged zone. The stem cells of muscles (myosatellitocytes) are mononuclear spindle cells that have typical organelles (including cell center), while their nuclei account for

10% of all nuclei of the muscle fiber and are similar to the nuclei of myosymplasts (Quintero et al., 2009; Pallafacchina et al., 2013). They are located in the cavity (groove) of the fiber and are covered with a common basal membrane (Mauro, 1961).

Stem cells normally remain in a "dormant" state, without dividing for many years until they are activated, for example, with tissue damage. They are extremely stable in such a state and remain viable for a long time under conditions of hypoxia and even after the death of the organism. That is, myosatellitocytes are a kind of "repair" system of muscle tissue and can provide a renewal of muscle tissue throughout life (Latil et al., 2012).

The number of satellite cells depends on many factors and is specific for individual muscles. For example, slow muscle fibers contain three to four times more satellite cells than fast muscle fibers, while masticatory muscle contains significantly fewer satellite cells than limb muscles (Rocheteau et al., 2015).

At the initial stages, the processes of myosatellitocyte activation are regulated by hepatocyte growth factors (HGF), fibroblast growth factor (FGF), transforming growth factor (TGF-β), insulin-like growth factor (IGF-1), tumor necrosis factor (TNF-α), etc. (Karalaki et al., 2009).

Under conditions of stable muscle homeostasis, myosatellitocytes are in a resting state and, correspondingly, have a low activity of metabolic processes, using lipids as a main source of energy (Fukada et al., 2007). However, long-term preservation of the viability of these cells under anaerobic conditions (even after human death) indicates that the peculiarities of energy supply of "dormant" myosatellitocytes require detailed study (Rocheteau et al., 2015).

As well as other stem cells, myosatellitocytes have the ability to maintain a stable amount in the tissue by asymmetric or mitotic divisions. During asymmetric division, two daughter cells are formed: one of them remains undifferentiated and retains the ability to reproduce itself, while the other undergoes differentiation and develops into a mature cell (Fuchs and Chen, 2012; Kumar et al., 2012). In healthy muscles, myosatellitocytes do not divide mitotically but are subject to asymmetric division and are used for regeneration in the zone of muscle damage (Brack and Rando, 2012). This provides the maintenance of a constant number of myosatellocytes. In regenerating muscles, the amount of undifferentiated cells increases along the periphery of damaged fibers due to mitotic division. At the same time, both daughter cells retain the ability to reproduce themselves (Fuchs and Chen, 2012). Thus, the ability of stem cells to two types of cell division is required to constantly maintain a certain number of them and efficient restoration of muscle damage (Pallafacchina et al., 2013; Rocheteau et al., 2015).

The direction of further transformations of these cells is determined by the level of expression of Pax3 and Pax7 transcription factors, myogenic determination factor (MyoD), Myf5, myogenin (Myf4), and MRF4 that are typical cell markers of resident stem cells. At rest, myosatellitocytes are characterized by high levels of expression of Pax7 and Myf5 transcription factors (Zammit et al., 2006; Le Moal et al., 2017; Yamakawa et al., 2020). After the activation (by damage, muscle inflammation), myosatellitocytes enter the cell cycle. At the beginning of their asymmetric division (formation of myoblasts), there is a high level of expression of Pax7 and Myf5 transcription factors as well as MyoD factor starts expressing. The beginning of the process of differentiation of myoblasts into myocytes and their fusion into myotubes with subsequent maturation in myofibrils is caused by a decrease in the levels of expression of Pax7, Myf5, and MyoD and an increase in the expression of MRF4 and myogenin (Myf4) factors (LeMoal et al., 2017; Schmidt et al., 2019; Yamakawa et al., 2020).

In addition to endogenous transcription factors, the activation of myosatellitocytes is also affected by other muscle tissue cells and their mediators. Loose connective tissue with multiple cells (macrophages, dendritic cells, tissue basophils (mast cells), pericytes, adipocytes, fibroblasts, endothelial cells, mesenchymal stem cells (FAPs), and other immune cells that, if necessary, can migrate from the vascular bed) is located between the muscle fibers and adjacent blood capillaries (in the interstitium) (Le Moal et al., 2017; Schmidt et al., 2019; Yamakawa et al., 2020).

The migration of myosatellitocytes to the damage area is one more necessary condition for ensuring rapid regeneration of muscle tissue. This movement occurs by the formation of cell wall protrusion and overflow of the cytoplasm (amoeboid movement). The movement of myosatellitocytes is regulated by nitric oxide (NO) through the appropriate signaling pathways (Anderson, 2000; Otto et al., 2011) as well as through a noncanonical Wnt signaling pathway (May-Simera and Kelley, 2012). In skeletal muscles, canonical Wnt signaling regulates the differentiation of satellite cells, while noncanonical is responsible for stimulating the mitosis of satellite cells and their migration. Cysteine-rich secretory glycoproteins are the effector molecules of the Wnt signaling pathway (Brack et al., 2007). Specific combinations of certain effectors and receptors of this pathway and NO-dependent mechanisms provide a fine regulation of movement and differentiation of myosatellitocytes that are required for a rapid regeneration of damaged muscle fiber. With age, the rate of myosatellitocyte movement decreases approximately two times. This is caused by a violation of their amoeboid movements and a low level of expression of growth factors and integrins (heterodimeric glycoproteins providing the adhesion between the cells and extracellular matrix of muscle tissue) (Mayer, 2003; Collins-Hooper et al., 2012).

After damage or injury, satellite cells switch from a resting state to an activated state, which is accompanied by significant rearrangements in the chromatin packaging of myosatellitocytes that are required for activating the transcription of the genes encoding proteins of the main pathways of energy supply and plastic metabolism. It is obvious that such global rapid switches of myosatellitocyte metabolism are accompanied by a rapid degradation of both excess cytosolic proteins and transcription factors that are unnecessary at certain stages of differentiation, which is provided by autophagy-lysosomal and ubictin-dependent systems of proteolysis (Blondelle et al., 2017).

As a result, metabolic pathways at rest and in activated and differentiated myosatellitocytes differ significantly from each other (Ryall, 2013; Tang and Rando, 2014; Dell'Orso et al., 2019; Nalbandian et al., 2020).

It is considered that chemical modifications of histones play a key role in such reorganization of the genetic apparatus and cell metabolism (Liu et al., 2013). For example, histone acetylation is associated with "open" chromatin and increased expression of the genes and is partially regulated by the presence of acetyl-CoA in the cytoplasm and nucleus (Moussaieff et al., 2015). $NAD^+$-dependent histone deacetylase (SIRT1) (the enzyme that cleaves an acetyl group from N-terminal histone sequences and uses $NAD^+$ as a cofactor) is another component of this mechanism of epigenetic regulation of metabolism (Jing and Lin, 2015; Nalbandian et al., 2020).

The transition of metabolism from fatty acid oxidation to glycolysis in activated myosatellitocytes is accompanied by a decrease in intracellular $NAD^+$ content (due to an increase in NADH) and, correspondingly, SIRT1 inactivation. Increased histone acetylation and triggering myogenesis are a consequence of this. It is logical to assume that lactate, which can convert directly to pyruvate (with the reduction of $NAD^+$ to NADH, which again will contribute to SIRT1 inactivation) is one of low molecular weight (indirect) regulators of metabolism and activation and differentiation of myosatellitocytes (Willkomm et al., 2014; Oishi et al., 2015). At the same time, it is necessary to take into account a potential role of lactate as a signaling molecule (Nalbandian et al., 2020), and myosatellitocytes located closer to the capillaries and vessels can be exposed to the effect of high concentrations of this energy-intensive metabolite with a submaximal physical exercise. Thus, the metabolic regulation of the activity of $NAD^+$-dependent histone deacetylase (SIRT1) can correlate metabolic changes (Bosch-Presegue and Vaquero, 2015) and epigenetic regulation of the processes in the stem cells (Fang et al., 2019).

In a number of works, the role of lactate in the development of muscle hypertrophy due to its effect particularly on these cells is proven on the model of experimental animals (Oishi et al., 2015). However, the mechanisms of the effect of lactate and their correlation with regulatory mechanisms that are activated with acute hypoxia require further study (Britto et al., 2020).

Protein kinase (AMPK), which is activated with an increase in the AMP/ATP ratio, is one more global regulator of metabolism and self-reproduction of myosatellitocytes (Hardie et al., 2012; Theret et al., 2017). Its activity increases with a decrease in the caloric content of the diet, which, in turn, improves the processes of regeneration in skeletal muscles (Canto and Auwerx, 2011; Cerletti et al., 2012).

It is known that limitation of caloric content of the diet increases the activity of stem cells and causes an increase in the number of mitochondria in muscle fibers (Cerletti et al., 2012; Abreu, 2020). Despite some controversy in the observed metabolic effects, it was proven on many animal models that limitation of caloric content of the diet prolongs the life expectancy (Marzetti, 2008; Abreu, 2020). The study of molecular genetic aspects of the effect of physical exercises and caloric content of the diet on metabolism of the muscle tissue is one of the fundamental questions of modern human biology.

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## COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest. This article contains no studies involving human participants and animals as objects of study.

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