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Role of myosin heavy chains in adaptive and pathological processes – a systematic review

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Abstract

Introduction: Myosin heavy chains (MHCs) are the core group of proteins that builds skeletal and cardiac muscle. Their characteristic is determined depending on MHC isoform, its percentage distribution and cross-sectional area of fibers it builds. These variables along with MHC gene expression undergo changes during adaptive and pathological processes.

Purpose: The aim of the article was to review significant studies on MHCs; summarize current knowledge in terms of adaptation, aging and pathological processes; provide interpretation and reach conclusions.

Methods: The literature review was conducted with topic-related articles found on platforms such as NCSI, PubMed, Google Scholar, using terms "MHC", "MYH", "Muscle adaptation", "myosin heavy chains" and "skeletal muscle" in the searching process.

Current Knowledge: During adaptation to physical activity, changes in MHCs are dependant on the type of activity. Endurance training decreases expression of MYH4 gene and increases expression of MYH7. It results in transformation of MHC II towards MHC I and in stimulation of mitochondrial biogenesis. Resistance training favors MHC IIa and hypertrophy. Aging process is associated with increased expression of MHC I but lifelong exercises help to preserve favorable fiber profile. MHC ratios and gene expressions are also altered in pathological conditions, such as obesity, neoplasms and heart disorders. MHCs play a significant role in fracture healing, and their serum levels may reflect soft tissue injuries.

Conclusions: MHC isoform distribution is associated with muscle adaptation and dysfunction. Understanding its regulation offers new perspectives in disease prevention, rehabilitation, and therapeutic strategies for muscle and cardiovascular health.

Keywords: Myosin heavy chains, muscle adaptation, aging, endurance training, resistance training

Introduction

Myosins are a superfamily of motor proteins, that consists of a head that binds actin and generates force through ATP hydrolysis, a neck composed of light chains (MLC) and a tail made of heavy chains (MHC) arranged in a double helix. Myosin heavy chains have a significant impact on the contractile properties of muscle what makes them an excellent research subject. Studies on the heavy chains of myosin were initiated in the 1960s and 1970s. Many approaches have been used to study them since then, such as measuring their specific force (SF) after removing membranes chemically (i.e. chemically skinned fibers), staining enzymes such as myosin ATPase, NADH-TR or succinate dehydrogenase (SDH), and immunohistochemical methods with different specific antibodies against MHC proteins [1]. Immunohistochemistry reagents for decades were based on polyclonal antibodies, but over the years were majorly replaced with highly specific monoclonal antibodies (mAbs), and synthetic peptide antigens [2].

In studies on mammals, several isoforms of heavy chains have been identified: MHC-α and β characteristic of myocardium, and differing in their distribution within the heart, encoded by the MYH6 and MYH7 genes; MHC15 (MYH15) and MHC-slow tonic (MYH7b), present in the extraocular muscles; MHC-neo (MYH8), involved in muscle regeneration; and two main myosin isotypes: slow-twitch type I (MHC I) and fast-twitch type II (MHC II), which are further divided into subtypes IIa, IIx (also known as IID), and IIb. It should be noted that MHC IIb subtype is absent in human muscles. MHC I and MHC II are products of the independent genes MYH7, MYH2, MYH1, and MYH4 [3].

Type I fibers are more resistant to fatigue due to the high density of mitochondria, while type II fibers are more glycolytic in metabolism, what translates to faster and more powerful contractions [2]. MHC IIa fibers are considered to be ~24% stronger than MHC I [1].
As a result, the distribution of the aforementioned fibers also differs according to the function of the muscle. A meta-analysis of 110 studies identified sex differences in body composition of skeletal muscle. Cross-sectional areas of all fiber types, as well as the percentage distribution and area of all MHC II subtypes, and the ratio of MHC II and MHC IIa to MHC I were greater in men than women. In contrast, women exhibited a greater percentage distribution and area of MHC I [4].

The amount of physical activity also affects the fiber composition. Specifically, as noted by a systematic review of 42 studies, 4 weeks of reduced activity (the median period for the studies) decreases the percentage content of MHC I in the vastus lateralis muscle by 2 percentage points and increases MHC IIx by 3 percentage points. Another thing one notices is a decrease in the cross-sectional area for both fibre types. At certain point these recomposition processes stabilize and no further changes in muscles occur [5].

Human pelvic and lower limb muscles, even after longstanding inactivity, are highly enriched in MHC I compared to living relatives - African great apes (gorillas, chimpanzees). This difference amounts to about 31% and indicates that our ancestors' content of MHC I may have been an evolutionary trait subject to selection in hominins [6].

Changes in MHC I versus MHC II proportions are also seen in conditions such as dilated and hypertrophic cardiomyopathy, fractures, or obesity. For example reduced ratio of type I to type II fibers in obesity is associated with a decreased ability to remove glucose, a lower content of mitochondria, and therefore a tendency to gain weight [9].

Although the actual post-translational modifications in MHC remain largely unknown, occurrence of this process have been reported in skeletal muscle and cardiac muscle in the last few years.. This indicates an additional mechanism for regulating cardiac muscle physiology. Modifications such as SUMO-ilation, phosphorylation, ubiquitination and acetylation may participate in the adaptation of MHC to changes in the conditions of the molecular and cellular environment of the heart. This potential role of these modifications motivates further research into this topic [7,8].

Myosin heavy chains in physical activity

MHC isoforms play a key role in determining the characteristics of muscle fiber types. Based on the expression of specific MHC isoforms, muscle fibers can be categorized into slow-twitch (type I with MHC I expression), fast-twitch oxidative-glycolytic (type IIa with MHC IIa expression) and fast-twitch glycolytic (type IIx with MHC IIx expression). Type IIb fibers, as previously mentioned are absent in humans; however, this MHC isoform is found in animals. The contraction speed of a given MHC isoform depends on amino acid changes in specific myosin-binding regions known as loops 2 and 3. The amino acid sequences in these loops affect myosin ATPase activity, which is higher in MHC II than in MHC I, enabling type II fibers to contract faster than type I fibers [10].

Adaptation to physical exercise in the form of MHC changes depends on the type of exercise. Endurance training, such as running and cycling, decreases MYH 4 expression and increases MYH 7 expression, causing a transformation of MHC II toward MHC I and an increase in the number of type I fibers, capable of slow and prolonged contraction. Studies suggest that endurance exercise influences MHC expression changes through the ROS/AMPK pathway and histone methylation remodeling. During exercise, there is an increased production of reactive oxygen species (ROS), which directly activate AMP-activated protein kinase (AMPK) through S-glutathionylation of the α and β subunits of AMPK. This leads to changes in AMPK kinase conformation and activity, resulting in enhanced phosphorylation. AMPK activation leads to increased expression of MLL and JMJD3 and decreased expression of JARID1B and EZH2. JMJD3 (Jumonji domain containing-3) is a demethylase that specifically transforms trimethylation of lysine 27 on histone H3 (H3K27me3) into less methylated forms, while EZH2 is a key component of the PRC2 (polycomb repressive complex 2) methylase complex, responsible for enriching specific gen promoters with H3K27me3.

JARID1B (Jumonji AT-rich interactive domain 1B), on the other hand, is a demethylase for H3K4me3 that requires oxygen molecules to carry out its catalytic activity. During endurance exercise, the level of beta hemoglobin increases, which additionally inhibits the activity of JARID1B by binding the oxygen needed by the enzyme. MLL (mixed lineage leukemia) is a key part of the COMPASS complex, which functions as a histone methyltransferase. Its main role is to increase H3K4me3 in gene promoters.

As a result of changes in the expression of these histone-modifying enzymes, there is a significant increase in H3K4me3 (associated with gene activation), along with no significant decrease in H3K27me3 (associated with gene repression) at the MYH7 promoter. Enzymatic activity changes also affect the MYH4 promoter, with a significant H3K27me3 enrichment and no significant change in H3K4me3 [10, 11]. Consequently, endurance exercise leads to an increased production of MHC I and a decreased synthesis of MHC II. Additionally, there is an increase in H3K4me3 and a decrease in H3K27me3 in the gene promoter of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which is responsible for regulating mitochondrial biogenesis, as well as the induction of expression of another mitochondrial content marker, cytochrome c oxidase subunit IV (COX IV). Other studies indicate that PGC-1α can be activated by sirtuin 1 (Sirt1), which is a product of AMPK activity, and the AMPK/Sirt1/PGC-1α pathway is closely related with conversion to type I fibers through an increase in the proportion of mitochondria [12]. This suggests that during adaptation to endurance training, there is a coupling of MHC I production with mitochondrial biosynthesis, leading to a transformation towards slow-twitch muscle fibers.

A significant role in this process is played by miRNAs, for example miR-499 [11]. miR-499 is encoded by the MYH7b gene, which is responsible for the expression of the slow isoform of MHC, and it contributes to increased production of proteins associated with slow-twitch fibers by inhibiting Sry-related high-mobility group box 6 (SOX6). Another important function of miR-499 is folliculin-interacting protein 1 (Fnip1) inhibition. It results in the activation of the AMPK-PGC-1α pathway, which as previously mentioned, regulates mitochondrial content in muscle fibers [10].

Studies on the effect of prolonged endurance training on muscle fiber composition show that individuals who have engaged in lifelong endurance exercise have a greater presence of MHC I compared to inactive individuals or those who exercise recreationally - the last two groups exhibit significantly lower amounts of MHC I. However, no significant differences in MHC IIa content were observed [13]. In resistance training, adaptation to exercise is connected to the transformation of muscle fibers towards fast-twitch type IIa and increased expression of MHC IIa. Some sources indicate the involvement of AMPK, which activity increases in both endurance and resistance training. AMPK stimulates the transformation towards IIx-IIa during the initial months of endurance and strength training [14].

Skeletal muscles during resistance training, such as weightlifting, are characterized by adaptation not only in the form of changes in MHC expression, but also in the form of hypertrophy, which is mediated by lactate produced in increased amounts during anaerobic exercise. Muscle hypertrophy occurs with the participation of satellite cells (SCs), which are activated in response to exercise and differentiate into myoblasts and generate the formation of new myofibrils in the process of muscle regeneration. This process is tightly regulated by the interaction of transcription factors such as Pax7 and myogenic regulatory factors (MRFs), which include myogenic factor 5 (Myf5), myogenic determinant protein (MyoD), myogenin and MRF4. In the resting state, Pax7 is present in SCs and acts as a regulator of MyoD. During exercise, when SCs are activated, increased expression starts from Myf5, then MyoD, myogenin and lastly MRF4 appear, which leads to final differentiation into new muscle fibers and production of specific structural and enzymatic proteins, including MHC.

It is not fully understood how lactate affects myogenesis, but it is suggested that it may modulate it by inducing MyoD expression. Lactate may also regulate myogenesis via mitogen-activated protein kinase (MAPK) by activating extracellular signal-regulated protein kinases (ERK1/2) and by inhibiting p38 MAPK. Additionally, lactate is capable of inducing creation of factors associated with muscle protein synthesis, including insulin-like growth factor 1 (IGF-1), protein kinase B (Akt) and the mammalian target of rapamycin (mTOR), along with its downstream target proteins in the signaling pathway- p70S6K and 4EBP1 [15].

Studies examining the impact of fatigue between sets of resistance training on changes in MHC and mTOR have shown that during exercises of moderate intensity, there is a more significant increase in the expression of MHC isoforms I and II (especially IIa) compared to exercises using a maximum number of repetitions. Although the Akt/mTOR pathway is linked to the induction of muscle protein synthesis, the study observed a slight decrease in mTOR levels in the muscles, likely due to adaptation to prolonged, repetitive strength exercises [16]. Furthermore, another study analysing the effect of fatigue during exercise sets found that individuals training to muscular failure experienced an increase in the phosphorylation of Ca2+/calmodulin-dependent protein kinase II δD (Phospho-Thr287-CAMKII δD), contrary to those training at lower intensities. The rise in Thr287-CAMKII δD phosphorylation, which regulates the expression of PGC-1α , positively correlates with muscle hypertrophy and the transformation of MHC IIx towards MHC IIa [17]. There are also analyses examining the correlation between the content of MHC IIa in the skeletal muscles of individuals engaged in resistance training with a focus on muscle strength. Research indicates that the mere amount of MHC IIa is not a definitive indicator of the strength that skeletal muscles can achieve during exertion. Muscle strength is influenced by other factors, such as the neuromuscular efficiency of the training individual, body fat content, and changes in enzymatic activity [18]. Studies show that individuals who have engaged in lifelong resistance training have a significantly greater number of muscle fibers expressing MHC II compared to those who engage in endurance training, and the quantity of type II fibers in these individuals at an advanced age is comparable to that of young people. Additionally, those who have trained in resistance exercises for many years also resemble younger individuals in terms of neuromuscular innervation and the number of atrophic fibers, in contrast to long-term endurance training [19].

Among the mechanisms responsible for muscle adaptation to physical exertion, molecular processes involving natural antisense transcripts (NAT) can also be distinguished. Research has shown that the regulation of gene expression encoding MHC is associated with the existence of NAT that encode antisense strands relative to these genes. In the absence of physical activity, which is characterized by a predominance of MHC IIx over other MHC isoforms, the expression of MHC IIx also induces the transcription of the antisense NAT for MHC IIa (aII NAT). Thus, the increase in the production of MHC IIx and the decrease in MHC IIa are correlated in the absence of physical activity. After a series of training sessions involving a combination of resistance and endurance exercises, an increase in the expression of MHC IIa was observed, accompanied by a simultaneous decrease in the transcription of aII NAT and a corresponding decrease in the expression of MHC IIx alongside an increase in the transcription of xII NAT, resulting in an increased ratio of MHC IIa to MHC IIx.

However, no significant differences in the content of MHC I were noted. This study therefore demonstrates the existence of coupled regulation of MHC synthesis through the coexpression of sense and antisense strands in bidirectional promoters [20].

Immobility leads to muscle atrophy and to transition of MHC isoforms in muscle fibers. In mice subjected to enforced immobility, there is a decrease in the expression of MHC I and MHC IIa, while the expression of MHC IIb increases. Additionally, disuse results in an imbalance between the breakdown of muscle proteins and their synthesis. Consequently, when immobility activates the protein degradation complex involving ubiquitin-proteasome, the IGF/Akt/mTOR signaling pathway responsible for protein synthesis is simultaneously inhibited leading to muscle atrophy in mice [21]. In addition, during periods of physical inactivity in men, F-box proteins associated with muscle atrophy (MAFbx) and MURF-1, which are E3 ubiquitin ligases responsible for the degradation of muscle proteins, are induced, and their expression is stimulated by forkhead box class O 3 (FoxO3) activated during muscle disuse. In addition, there is an increase in the expression of calsarcin-2, an inhibitor of calcineurin, which together with the nuclear factor of activated T cells (NFAT) stimulates the expression of proteins associated with switching fibers towards a slow phenotype. Inhibition of PGC-1α that occurs during immobility also inhibits the formation of MHC I fibers, while dephosphorylation of AMPK stimulates differentiation towards MHC II fibers [10].

The cardiac muscle also adapts to physical exercise in the context of the expression of MHC isoforms. The molecular mechanism of adaptation involves, among others, non-coding mRNAs, for example miR-222 contributes to physiological hypertrophy of the cardiac muscle in response to increased exercise in the form of an increase in the ratio of MHC-α to MHC-β [22]. Physical exercise also inhibits CCAAT/enhancer binding protein (C/EPBβ) and increases the expression of ED-rich carboxyl-terminal domain 4 (CITED4). βC/EPBβ reduces transcription of cardiac genes such as MHC-α by interacting with serum response factor (SRF) binding to gene promoters. Thus, inhibition of C/EPBβ by exercise leads to increased MHC-α expression and physiological myocardial hypertrophy [23].

Numerous studies demonstrate differences in adaptation to physical exertion between men and women. In sedentary individuals, the distribution of MHC isoforms in the muscles is very similar for both sexes. Despite this similarity, inactive men exhibit greater muscle contraction strength, likely due to better cross-bridge kinetics of MHC II [24]. One analysis examined the differences between men and women engaged in weightlifting and a control group. The weightlifters had a higher number of fibers expressing MHC I and MHC IIa, while the control individuals had more MHC IIx fibers. Among the research samples, women displayed greater expression of MHC IIa in response to resistance training compared to men [18]. A similar finding was observed in another study that analyzed MHC differences between American professional weightlifters of world-class and national caliber. Women of world-class caliber demonstrated the highest expression of MHC IIa, while both men and women of national caliber expressed lower levels of MHC IIa [25]. In a study investigating the differences in adaptation between the sexes during mixed training that included elements of endurance and strength exercises, no significant differences in MHC expression were found in men and women, except for pre-mRNA MHC IIx.

Men showed decreased expression of pre-mRNA MHC IIx, while women exhibited increased expression, which may result from the lower amount of MHC IIx in women before training and the normalization of these differences following training [20].

Myosin heavy chains – age related variability

With age, changes occur in the structure and function of muscles that lead to declines in maximum generated strength and power and to loss of muscle mass. Declines in strength and power are proven to be disproportionately greater than the loss of muscle mass, despite strong connection between these two processes [26]. Various causes of this phenomenon are proposed, related to mechanisms occurring within the muscle and a decrease in voluntary muscle activation with age. A 2020 meta-analysis found that these changes are mainly of intramuscular origin and voluntary activation only slightly decreases with age, but still might be the cause of certain disproportion between the loss of strength and power and the loss of muscle mass [27]. Intramuscular origin as the main factor is supported by the close relationship between the level of maximum power and the loss of lean thigh tissue mass thus including the changes in the composition and structure of MHC discussed in this work [28]. Along with the aging process no changes in the size and contractile function of MHC I are observed, but there is a significant increase of MHC I expression in older individuals. In contrast, fast-twitch MHC II and MHC IIa undergo atrophy, leading to a reduction in their size and expression. However, the distribution of fibers remains unchanged [26, 29]. It should be noted that age-related changes are partly due to decreased physical activity, which leads, for example, to a decline in the content of MHC I in the vastus lateralis muscle by approximately 2 percentage points, alongside an increase in MHC IIx by about 3 percentage points and a reduction in the cross-sectional area of both types of fibers. Atrophy of fibers is greater for all types of MHC II than for MHC I. In individuals confined to bed rest, greater losses in the cross-sectional area of fibers have been observed compared to those who simply stop training. This parallels the situation of many immobilized older adults across the world. However, it is important to remember that changes in structure due to this reason only occur up to a certain point, after which the muscle stabilizes [5]. The overall increase in the proportion of slow-twitch MHC I in relation to fast-twitch MHC II accounts for the slowed rate of strength development of the entire muscle, prolonged relaxation time, and a higher frequency of injuries during sudden movements [26, 29].

The described changes and sarcopenia can be partially prevented through a proper diet and prolonged, regular physical activity. Endurance exercise has been investigated in this context by studying older individuals (aged 70-78) who have engaged in endurance training for their entire lives (a minimum of 50 years of exercise). MHC I expressed by people from this group were approximately 40% bigger, 10% faster, 20% stronger and 30% more efficient compared to two other groups: healthy individuals aged 73-77 leading a sedentary lifestyle and active young people (~25 years old). While the study did not observe an effect of endurance exercise on MHC II, a difference was noted in the mechanics of MHC I depending on the intensity of the exercises performed. People who had been exercising for many years were divided into two smaller groups, i.e. those exercising moderately for physical fitness and those taking part in competitions.

An increase in power output was observed in both groups, but partially through different mechanism. While moderate exercisers showed an increase in force, athletes experienced an increase in velocity [30]. This finding relates to another study that examined the impact of resistance training on muscle fibers. Resistance training proved to be more effective, having a greater influence on MHC II than the aerobic training described above. It leads to significantly greater hypertrophy of MHC II compared to MHC I (23% vs. 8%) [31].

Additionally, for older individuals with sarcopenia and those trying to prevent it (including individuals with Parkinson's disease), appropriate muscle-targeted supplementation (MT-ONS) is recommended in conjunction with resistance exercises. This includes the consumption of high-quality protein, such as whey protein, as well as the supplementation of vitamin D. Such actions, even without a physical activity component, lead to improvements in clinical outcomes. However, it is important to note that further analyses are needed to assess the impact of supplementation on specific groups, such as patients with significant muscle mass loss, older individuals who are malnourished, as well as observed changes in muscle size and structure in terms of MHC [32].

Myosin heavy chains in disease

The healing rate of fractures and its effectiveness are closely related to the integrity of the surrounding soft tissues, indicating that muscle mass accelerates the fracture healing process. This is primarily due to increased blood flow from muscle activity, which drives the transport of nutrients, that are used by mesenchymal stem cells, in the fractured bone [33]. Myosin has enzymatic activity associated with muscle contraction and maintains the structural integrity of muscle cells. Furthermore, it has the ability to enhance the formation of blood clots, which initially serve as a scaffold for further healing processes after a bone fracture. MHC in skeletal muscle influence the blood coagulation process through a unique mechanism of interaction with factor XI (FXI) in the intrinsic coagulation pathway. MHC promote the formation of clots in response to exposure to circulating blood, and consequently, to the coagulation factors present within it [34, 35]. Studies have confirmed a tendency for the formation of fibrin-rich clots on the surface of MHC, with factor XI playing a significant role; experimental inhibition of this factor notably reduced this effect [33]. Factor XI possesses several domains, of which domains A3 and A4 are the key, displaying the highest affinity for MHC, thus enabling its stabilization at the site of coagulation. Furthermore, the action of MHC is unique in that it remains independent of the anionic phospholipid and polyphosphate pathways, which also act as cofactors for the activation of factor XI. The described properties of MHC highlight its crucial role in the formation of clots at fracture sites, which serve as a precursor for further rebuilding. Fibrin present in the clot provides a scaffold to which progenitor cells and mesenchymal stem cells necessary for bone regeneration adhere [36]. Additionally, it releases chemical signals, primarily VEGF, which stimulates angiogenesis, as well as PDGF (platelet-derived growth factor) and BMP (bone morphogenetic proteins), which enhance the differentiation of progenitor cells into osteoblasts [37]. In the next stages, collagen and hydroxyapatite, which are key components of the bone matrix, are deposited [38].

The role of MHC in bone reconstruction does not end with the formation of clots. MHC expression has also been shown in the callus of broken bones, even to a degree that exceeds its quantity in thrombi. The callus itself is a thick-fibrous, primary bone tissue that develops in the focus of bone damage or fracture, striving to heal it. Proteomics and liquid chromatography combined with mass spectrometry have shown significantly increased MHC expression in the callus. [39]. In vitro studies using soluble MHC II for the treatment of chondrocytes have shown a significant increase in osteogenic markers MMP13 and RUNX2. MMP13 (matrix metalloproteinase 13) and its high expression in human mesenchymal stem cells (hMSCs) promotes osteogenic differentiation and thus the development of osteoblasts. Moreover, it acts through a specific feedback loop on RUNX2 - a transcription factor associated with osteoblast differentiation, which in turn is a regulator of genes associated with osteogenesis, such as type I collagen, osteocalcin or osteopontin genes. It is also responsible for the increased expression of integrin α3 (ITGA3) and activation of FAK, and through this it supports the process of mineralization and the formation of new bone tissue and, continuing the positive feedback loop, increases the expression of MMP13 [40].

The level of myosin heavy chain (MHC) concentrations in the serum of patients following injuries and procedures involving the musculoskeletal system is more significant [41]. An increase in MHC levels may indicate damage to the contractile apparatus of the muscles [42]. Besides the temporal rise in MHC correlated with injury and surgical intervention, it can also have long-term prognostic implications due to the sustained elevated levels in serum resulting from muscle damage [43]. This allows for both late-stage diagnostics and prognostic assessments. MHC levels were evaluated in patients preoperatively and postoperatively, as well as in patients in the early phase of soft tissue injury, using monoclonal antibodies that bind to β-type MHC. Samples were collected from 31 trauma patients upon hospital admission, as well as from 13 healthy individuals as a control group. In the control group, the mean level of MHC was 75±47 (μU/L) with a median of 65. While no specific changes were noted in the serum of individuals with soft tissue injuries compared to the control group, in post-operative patients, the mean MHC concentration was 305±38, with a median of 120. Moreover, in serum collected prior to the procedure, MHC levels were elevated compared to the control group, with a median of 96 [44]. These results indicate a correlation between musculoskeletal system damage and an increase in MHC, suggesting the potential use of MHC as biomarkers for the degree of soft tissue injury [45][46].

It has been proven that pathogenesis of heart failure is significantly influenced by MYH7 gene. It encodes cardiac β-myosin in cardiomyocytes, so it is essential for the proper functioning of the heart, and genetic disorders associated with this gene result from its mutation or complete absence [47]. Mutations in the MYH7 gene affect the tendency to develop dilated and hypertrophic cardiomyopathies, which can lead to complications such as heart failure [48]. These mutations are also associated with other cardiac pathologies, such as left ventricular non-compaction, bicuspid aortic valve (BAV), and myocarditis [49]. A study was conducted in which heterozygous pathogenic variants in the MYH7 gene were identified in families with cardiomyopathy, left ventricular no-ncompaction (LVNC), and congenital heart disease (CHD), usually in the form of septal defects or Ebstein anomaly and univentricular heart disease with heart failure.

These results motivated a subsequent study in which three patients with a history of CHD, LVNC and arrhythmia were investigated and the presence of MYH7 variants was confirmed by multigene testing or exome sequencing. In order to confirm the influence of heredity and thus to prove the genetic origin of these diseases, 12 affected family members were found in these three patients: four had Ebstein anomaly and seven had a history of LVNC. These observations suggest a wide phenotypic spectrum of heart defects associated with MYH7 [50].

A study using whole-genome sequencing was performed to identify MYH7 gene variants in 397 patients with different subtypes of cardiomyopathy, characterized by hypercontractility, poor relaxation, and increased energy expenditure. In silico analyses were also performed to assess the potential pathogenicity of the newly identified variants, comparing them with previously known pathogenic variants. Twenty-seven MYH7 variants were identified in 41 unrelated patients with cardiomyopathy, including: 20 previously known pathogenic or likely pathogenic variants, 2 variants of uncertain clinical significance (VUS) and 5 newly discovered variants. The newly identified variants were considered potentially pathogenic, as confirmed by high scores in in silico analyses [51]. Other studies, in addition to MHC7 mutations, point to the MYBPC3 gene as one of the factors of heart disease [52]. In this case, it leads to increased myosin contractility and a shift in the proportion towards disturbed conformation (DRX), which, by enabling greater ATP consumption, allows for more intensive heart work but worsens their relaxation, inducing hypertrophic cell remodeling and increasing energy stress. In the relaxed state, the myosin head domains form a motif of interacting heads, which allows the adoption of super relaxed conformation (SRX), in which both ATP-binding domains are sterically blocked and cannot bind actin, maximizing energy savings, or a disturbed conformation. The hemodynamic requirements of the organism, pharmacological myosin modulators and pathogenic myosin point mutations affect the proportions of these conformations. For example, hibernation, in which tissues significantly reduce their activity and energy consumption to survive periods of extreme cold or food scarcity, increases the proportion of myosins in the SRX conformation, while pathogenic variants of genes, as in the case of MYBPC3, destabilize this balance, increasing the percentage of myosins in the DRX conformation [53]. In left ventricular noncompaction disease (LVNC), the abnormalities result from a new pathological variant of MYH7 (p.Leu655Met) revealed by a study in the genome of related individuals. It acts by disrupting the binding of actin to myosin, which leads to defects in heart wall morphogenesis. These studies also found that this particular variant exhibited an autosomal dominant inheritance pattern and was present in all family members studied [54].

Mutations in the nonmuscle myosin heavy chain 9, encoded by the MYH9 gen, in viral and neoplastic diseases have also been found [55]. MYH9 product physiologically participates in cell adhesion by facilitating the formation of intercellular junctions, in cell polarization and migration due to remodeling of the actin cytoskeleton, and in cell division by forming a contractile ring during cytokinesis [56]. In viral diseases, it is a receptor for pathogen binding proteins. In the case of HSV-1, it binds the glycoprotein gD of the virus and enables its fusion with the membrane, while for EBV it is a gateway to the host cells by combining with glycoproteins gH or gL [57].

The MYH9 mutation also facilitates infection for the SARS- CoV- 2 virus. Its action consists in combining myosin heavy chain 9 with the S1 and S2 subunits located on the spikes of the virus, thereby facilitating their binding to human ACE2, thus enabling the fusion of the virus with the host membrane and, in the next stage, its internalization through endocytosis [58]. The role of MYH9 in cancer formation turns out to be unclear. In mouse models, the MYH9 mutation acts as a suppressor for skin or squamous cell carcinoma of the head's skin, but in human tumors it shows strong promoter properties by supporting proliferation, dissemination, invasion of distant cells and even stimulating resistance to therapy. At the molecular level, it acts by promoting tumor signaling pathways - Wnt/β-catenin, PI3K/AKT, MAPK, and on the other hand by stabilizing oncogenes, e.g. c-Myc and inhibiting suppressor proteins - p53 [59].

Conclusion

MHC are the basic proteins of skeletal and cardiac muscles, playing a fundamental role in their function. Their diverse isoforms determine the contractile properties of muscles, influencing the force of contraction, the speed of contraction and resistance to fatigue. Changes in MHC ratios occur as a result of physical activity, aging of the organism and various pathological conditions, making them an important factor in muscle adaptation to physiological conditions and disease.

Routine physical exercise, both strength and endurance, shapes muscle composition by regulating MHC expression. Endurance exercise promotes a change in fibers towards slow twitch, through their increased resistance to fatigue and oxygen metabolism of fibers. Strength training, on the other hand, favors the development of fast twitch fibers, which increases their strength and muscle mass. They depend on molecular mechanisms, such as the AMPK and PGC-1α signaling pathways, which affect the expression of genes responsible for MHC composition and mitochondrial biogenesis. Muscular adaptation to physical exercise demonstrating as MHC isoform changes are different for women and men, with women displaying greater MHC IIa expression during resistance training. In a sedentary state, both sexes exhibit a similar distribution of MHC isoforms.

Aging leads to a gradual reduction in muscle mass and function, to which heterogeneity of MHC expression has contributed to some extent. With age, the share of slow-twitch fibers increases to the detriment of fast-twitch fibers, which results in a decrease in strength and contraction speed. This process can be inhibited by systematic physical activity, especially strength training, which helps maintain muscle mass and contractility. During this time, proper nutrition, especially protein and vitamin D supplementation, can participate in muscle growth and limit the effects of sarcopenia.

Abnormalities in MHC proportions are also associated with many diseases. Mutations in the MYH7 gene encoding MHC in the cardiac muscle are associated with dilated and hypertrophic cardiomyopathies and lead to ischemic heart disease. Disturbances in MHC composition in skeletal muscle may promote obesity and limit the ability of muscles to metabolize glucose and fats effectively. In addition, MHC are responsible for regenerative processes, acting on fracture healing processes along with interaction with coagulation factor and activating angiogenesis and new bone formation.

In summary, MHC are the main regulators of muscle function, and their expression and modifications are significant in adaptation to physical exercise, aging processes, and pathogenesis of many diseases. Understanding the mechanisms of their functioning may encourage the creation of better treatment and prevention strategies in terms of ensuring muscle and circulatory system health.

Disclosure

Author's contribution

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