

Review article

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Molecular Mechanisms Underlying Skeletal Muscle Adaptation to Exercise: From Signal Transduction to Functional Remodeling

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Skeletal muscle adaptation to exercise involves a complex network of molecular signaling pathways that regulate energy metabolism, protein synthesis, mitochondrial biogenesis and cellular remodeling. This review provides a comprehensive overview of key molecular mechanisms underlying both endurance and resistance training responses, focusing on central regulators such as AMP-activated protein kinase (AMPK), mechanistic target of rapamycin complex 1 (mTORC1), calcium/calmodulin-dependent protein kinase (CaMK), and transcriptional coactivators like peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α). Special attention is given to the influence of age and sex on adaptive capacity. Age-related anabolic resistance and sarcopenia are linked to impaired mTOR signaling, chronic inflammation, and mitochondrial

dysfunction, while sex-specific hormonal profiles modulate transcriptional and metabolic responses to exercise. Additionally, biomarkers such as creatine kinase, C-reactive protein, myokines (interleukine-6, PGC- α , myostatin) and microRNAs, are emerging tools for monitoring adaptation and recovery. Future research should prioritize multi-omics integration, digital biomarkers, and longitudinal human studies to understand the complexity of muscle remodeling. Understanding molecular mechanisms behind exercise adaptation will enhance the design of targeted interventions for athletic performance and rehabilitation advancing the field of precision exercise medicine.

Keywords: Muscle adaptation, Exercise, AMPK, mTORC1, PGC-1 α

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Molekularni mehanizmi adaptacije skeletnih mišića na vežbanje: od signalne transdukcije do funkcionalnog remodelovanja

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Adaptacija skeletnih mišića na fizičku aktivnost uključuje složenu mrežu signalnih puteva koji regulišu energetske metabolizam, sintezu proteina, mitohondrijalnu biogenezu i ćelijsko remodelovanje. Ovaj pregledni rad pruža sveobuhvatan uvid u najznačajnije molekularne mehanizme koji omogućavaju adaptaciju na trening izdržljivosti i trening snage, sa fokusom na centralne molekularne regulatore kao što su AMP-aktivirana protein kinaza (AMPK), mehanistički cilj rapamicina kompleks 1 (mTORC1), kalcijum/kalmodulin-zavisna protein kinaza (CaMK) i transkripcioni koaktivatori poput peroksizom-proliferator-aktiviranog receptora gama koaktivatora 1-alfa (PGC-1 α). Posebna pažnja posvećena je uticaju starosti i pola na adaptivni kapacitet skeletnih mišića. Anabolička rezistencija u starosti i sarkopenija povezane su sa poremećajem mTOR signalizacije, hroničnom inflamacijom i mitohondrijalnom disfunkcijom, dok hormonski profili specifični za pol

modulišu transkripcione i metaboličke odgovore na vežbanje. Pored toga, biomarkeri kao što su kreatin kinaza, C-reaktivni protein, miokini (interleukin-6, PGC- α , miostatin) i mikroRNK dobijaju na značaju u praćenju adaptacije i oporavka skeletnih mišića. Buduća istraživanja treba da obuhvate integraciju multi-omika pristupa, digitalnih biomarkera i longitudinalnih kliničkih studija u cilju boljeg razumevanja kompleksnosti remodelovanja mišića. Razumevanje molekularnih mehanizama u osnovi adaptacije na vežbanje moglo bi da omogući unapredjnje dizajna ciljanih intervencija u cilju unapređenja sportskih performansi i rehabilitacije, doprinoseći razvoju personalizovane sportske medicine.

Ključne reči: adaptacija mišića, vežbanje, AMPK, mTORC1, PGC-1 α

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Introduction

Modern lifestyles are characterized by prolonged periods of physical inactivity, leading to a global rise in multiple chronic diseases such as type 2 diabetes mellitus, obesity, cardiovascular disease, and their complications (1–3). Sedentary behavior is associated with impaired mitochondrial function, reduced insulin sensitivity, and chronic low-grade inflammation, all of which negatively impact skeletal muscle health and systemic homeostasis (3,4). In contrast, regular physical activity induces a wide array of beneficial adaptations in skeletal muscle, including enhanced oxidative capacity, improved glucose metabolism, and increased protein synthesis (5,6). These adaptations are mediated by tightly regulated molecular mechanisms that respond to mechanical, metabolic, and hormonal stimuli (6).

Skeletal muscle is a remarkably plastic tissue capable of adapting to various physiological demands, particularly those imposed by different forms of exercise (5–7). This adaptability is not only essential for athletic performance but also plays a critical role in maintaining metabolic well-being, flexibility, and resistance to aging and chronic illness. Exercise-induced muscle adaptation encompasses a spectrum of structural and functional changes, including hypertrophy, mitochondrial biogenesis, angiogenesis, shifts in muscle fiber type composition, and metabolic reprogramming (5,6). These adaptations are driven by complex signaling pathways converting external signals into particular transcriptional and translational programs (8).

Resistance training primarily promotes protein synthesis and muscle hypertrophy (9). These effects are largely mediated by the mammalian target of rapamycin (mTOR) signaling pathway that is activated by mechanical stress and growth factors like insulin-like growth factor 1 (IGF-1), which drives anabolic signaling and satellite cell activation eventually leading to strength gain (9,10).

In contrast, endurance training stimulates mitochondrial biogenesis, improves oxidative capacity, and enhances capillary density through energy-sensing pathways involving AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), and NAD-dependent deacetylase sirtuin-1 (SIRT1) (11,12). The resulting increase in the numbers and functionality of mitochondria supports efficient ATP production and provides metabolic flexibility.

Angiogenesis is another important adaptation to endurance exercise stimulated by hypoxia-induced expression of vascular endothelial growth factor (VEGF) and other angiogenic mediators (13). It increases the delivery of oxygen and nutrients to active muscle fibers and aids aerobic metabolism and mitochondrial action.

Changes in muscle fiber type composition are also effects of exercise. Endurance exercise induces conversion to more oxidative type I fibers, while resistance training is more likely to maintain or increase the size of type II fibers (14). These changes are regulated by calcium-dependent signaling, such as calcineurin/ nuclear factor of activated T-cells (NFAT) (14).

High-intensity interval training (HIIT), which combines elements of both resistance and endurance modalities, improves aerobic capacity, insulin sensitivity, and mitochondrial function (15). Although HIIT promotes mitochondrial biogenesis, it can lead to hypertrophy, although to a lesser extent than resistance exercise (16).

Muscle adaptations to exercise can be acute and chronic (17,18). Acute responses take place immediately after an exercise session and include changes in gene expression, enzyme activity, and metabolite concentrations. Chronic adaptations occur with regular training and involve alterations in structural protein synthesis and muscle remodeling. However, individual factors such as age, sex, and genetic background significantly influence the adaptability of skeletal muscle to exercise (19,20).

This narrative review aims to summarize the molecular mechanisms underlying skeletal muscle adaptation to different types of exercise, including resistance, endurance, and HIIT. Special focus is given to human research that includes transcriptomic, proteomic, and epigenetic data. As well as influences of sex differences and ageing on adaptive responses.

Methods

In preparation of this narrative review, we performed PubMed and MEDLINE database search for articles published in English over the past five years. The following search string was used: ("muscle adaptation"[Title/Abstract] OR "skeletal muscle plasticity"[Title/Abstract]) AND ("exercise"[Title/Abstract] OR "physical activity"[Title/Abstract]) AND ("molecular

mechanisms"[Title/Abstract] OR "signal transduction"[Title/Abstract] OR "gene expression"[Title/Abstract] OR "epigenetics"[Title/Abstract] OR "transcriptional regulation"[Title/Abstract] OR "protein synthesis"[Title/Abstract] OR "mitochondrial biogenesis"[Title/Abstract] OR "hypertrophy"[Title/Abstract] OR "AMPK"[Title/Abstract] OR "PGC-1 α "[Title/Abstract] OR "mTOR"[Title/Abstract]). The search yielded 51 articles, including 24 review articles. After title/abstract and full text screening, we identified the papers relevant to the scope of this review. Additionally, bibliographies of included papers were also searched for relevant articles.

Background

Mechanical Stress and Resistance Training

Resistance training exerts mechanical stress on skeletal muscle fibers, activating signaling pathways that lead to hypertrophy and increased strength (21). The conversion of mechanical signals into biochemical responses that control gene expression, protein synthesis, and muscle remodeling is known as mechanotransduction (22). The mTOR, Hippo, and FAK signaling pathways are interconnected in the regulation of skeletal muscle adaptation, particularly in response to mechanical stimuli such as exercise.

The key signaling pathway that supports muscle growth induced by resistance training is the mTOR pathway (Figure 1). The mechanical stress stimulates the release of IGF-1 that binds to its receptor and activates phosphoinositide 3-kinase (PI3K). This causes phosphorylation and activation of the Akt kinase that stimulates anabolic signaling by activating the mechanistic target of rapamycin complex 1 (mTORC1). The downstream signaling of the mTORC1, which involves 70S6 kinase and 4E-BP1, significantly increases protein synthesis and leads to muscle hypertrophy (16,22–24). FoxO transcription factors are also suppressed by this pathway, thereby reducing expression of muscle atrophy-related genes like atrogen-1 and muscle ring-finger protein-1 (MuRF1) (25). mTOR-induced FoxO suppression enables preserving muscle mass.

. Signaling mechanisms involved in skeletal muscle adaptation to different training types.

Resistance training activates anabolic pathways such as AKT/mTOR, promoting protein synthesis and hypertrophy. Myostatin acts as a negative regulator via Smad signaling. Endurance and HIIT primarily engage AMPK–SIRT1–PGC-1 α axis and calcium-dependent signaling (CaMKII, Calcineurin, NFAT) contribute to the mitochondrial biogenesis and oxidative metabolism. The Figure is made using vectors by Servier Medical Art (available on <https://smart.servier.com/>), licensed under a CC BY 4.0.

Abbreviations: AKT – Protein kinase B, AMP/ATP – adenosine monophosphate/adenosine triphosphate ratio, AMPK – AMP-activated protein kinase, Ca²⁺ – Calcium ion, CaMKII – Calcium/calmodulin-dependent protein kinase II, FoxO – Forkhead box O transcription factors, IL-6 – Interleukin-6, mTOR – Mechanistic target of rapamycin, NADH/NAD – nicotineamide adenine dinucleotide reduced/nicotineamide adenine dinucleotide oxidized ratio, PGC-1 α – Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, SIRT1 – Sirtuin 1, Smad – Mothers against decapentaplegic homolog proteins

Satellite cells are stem cells found in muscles that play an important role in muscle growth and regeneration. Mechanical and biochemical signals, such as IGF-1, stimulate the activation of satellite cells by resistance training (10,26). When activated, these cells proliferate and merge with existing muscle fibers, thereby increasing the number of myonuclei within the cells (10). The increase in mononuclear numbers facilitates transcription and protein synthesis, which is essential maintenance of hypertrophy, particularly in response to overload. The Notch signaling pathway and Pax7 expression are important regulators of satellite cells activation (27).

The Hippo pathway effectors, yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), function as mechanosensitive regulators of muscle growth (22,28). These proteins are receptors to cytoskeletal tension and extracellular matrix stiffness, which upon activation translocate to the nucleus and activate cell proliferation and differentiation (29).

Extracellular matrix is linked to the cytoskeleton through focal adhesion complex, especially integrins, which function as mechanoreceptors. They stimulate focal adhesion kinase (FAK), a 125 kDa non-receptor tyrosine kinase that crosslinks mechanical signals with both mTOR and Hippo pathways (30).

Key molecules involved in AKT/mTOR/ FoxO Axis and mechanosensitive signaling pathways regulating skeletal muscle adaptation to exercise are listed in Table 1.

Table 1. Key molecules involved in major signaling pathways regulating skeletal muscle adaptation to exercise.

Pathway	Key Molecules	Training Type	Role in Adaptation
PI3K/AKT/mTOR Axis	Akt, mTOR, 70S6K, 4E-BP1	Resistance Training	Promotes protein synthesis, hypertrophy
PI3K/AKT/mTOR/ FoxO Axis	FoxO, atrogin-1 MuRF1	Resistance Training	Suppresses atrophy genes
PI3K/AKT/mTOR/ IGF-1 Axis	IGF-1	Resistance Training	Satellite cells regulation, muscle regeneration and hypertrophy
Wnt/Notch/Pax7 axis	Pax7, Notch, Wnt	Resistance Training	Satellite cells regulation, muscle regeneration and hypertrophy
Myostatin-Smad Pathway	Myostatin, Smad2/3	Resistance Training	Negative regulator of muscle growth, reduced by resistance exercise
Hippo pathway	YAP, TAZ	Resistance Training	Mechanosensitive regulators, stimulating muscle growth
AMPK-SIRT1-PGC-1 α Axis	AMPK, SIRT1, PGC-1 α , Nrf1, Nrf2, TFAM	Endurance Training, HIIT	Energy sensing, mitochondrial biogenesis, oxidative metabolism
Calcium Signaling	CaMKII, Calcineurin, NFAT, CREB, PGC-1 α	Endurance Training, HIIT	Fiber type specification, oxidative metabolism
ROS / Antioxidant Response	Nrf2, SOD, GPx, catalase	Moderate or high intensity resistance and endurance training, HIIT	Antioxidant defense, stress adaptation
Inflammatory Pathways	NF- κ B, TNF- α , IL-6, IL-1 β	Moderate or high intensity resistance and endurance training, HIIT	Acute inflammation for adaptation, chronic inflammation detrimental

Abbreviations: AMPK – AMP-activated protein kinase; Akt – Protein kinase B; CaMKII –

Calcium/calmodulin-dependent protein kinase II; CREB – cAMP response element-binding protein;

FoxO – Forkhead box O transcription factors; GPx – Glutathione peroxidase; HIIT – High-intensity interval training; IGF-1 – Insulin-like growth factor 1; IL – Interleukin (IL-1 β , IL-6, etc.); mTOR –

Mechanistic target of rapamycin; mTORC1 – Mechanistic target of rapamycin complex 1; MuRF1 –

Muscle ring finger protein 1; NF- κ B – Nuclear factor kappa-light-chain-enhancer of activated B cells;

NFAT – Nuclear factor of activated T-cells; Nrf1 – Nuclear respiratory factor 1; Nrf2 – Nuclear factor

erythroid 2-related factor 2; PGC-1 α – Peroxisome proliferator-activated receptor gamma coactivator

1-alpha; PI3K – Phosphoinositide 3-kinase; Smad – Mothers against decapentaplegic homolog

proteins; SIRT1 – Sirtuin 1; SOD – Superoxide dismutase; TAZ – Transcriptional coactivator with PDZ-

binding motif; TFAM – Mitochondrial transcription factor A; TNF- α – Tumor necrosis factor-alpha; YAP – Yes-associated protein.

Metabolic Stress and Endurance Training

The metabolic requirements during endurance exercise led to adaptive responses that increased oxidative capacity, fatigue resistance, and metabolic flexibility in skeletal muscles. These adaptations are mediated by energy-sensing and redox-sensitive signaling pathways that regulate mitochondrial biogenesis, angiogenesis, and antioxidant defenses (6,31–33)

The AMP-activated protein kinase (AMPK), which acts as a cellular energy sensor, is a key regulator of endurance-induced muscle adaptation (Figure1). Increased AMP/ATP ratios activate AMPK during prolonged or intense exercise and initiate catabolic processes to restore energy balance ((34). AMPK phosphorylates and activates PGC-1 α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), which acts as a regulator of mitochondrial biogenesis and angiogenesis (6,33).

PGC-1 α coactivates nuclear respiratory factor 1 (NRF-1), nuclear factor erythroid 2-related factor 2 (NRF-2), and mitochondrial transcription factor A (TFAM), stimulating the expression of mitochondrial genes and mitochondrial biogenesis (35,36). This leads to an increased number of mitochondria, improved ATP generation, and enhancements in endurance performance.

A variety of factors activated by extracellular stimuli, including stress, exercise, or cytokines, contribute to the regulation of PGC-1 α . The transcription of PGC-1 α is enhanced by forkhead box class-01 (FoxO1) and cyclic AMP response element-binding protein (CREB) (36). In addition, nuclear factor-kappa B (NF- κ B) and mediators of inflammation, such as tumor necrosis factor α (TNF α), interleukin-4, and interferon- γ , also influence the expression of the PGC-1 α gene (6,36).

Exercise increases intracellular NAD⁺ levels, activating Sirutin 1 (SIRT1) and promoting mitochondrial biogenesis and antioxidant defenses (37–39). SIRT1 also interacts with FOXO transcription factors and stimulates the expression of genes involved in antioxidative defenses (40). In the PGC-1 α -dependent

pathway, SIRT1 initiates the activation of PGC-1 α via deacetylation (36). Once activated, PGC-1 α functions as a coactivator for mitochondrial transcription factor A (TFAM), which facilitates the transport of SIRT1 and PGC-1 α into the mitochondria, where they establish a complex that affects replication and transcription of mitochondrial DNA (36).

Increased mitochondrial biogenesis enhances oxidative phosphorylation and supports energy production during aerobic exercise, thereby contributing to endurance during exercise.

Key molecules involved in AMPK-SIRT1-PGC-1 α Axis regulating skeletal muscle adaptation to exercise are listed in Table 1.

Calcium Signaling

Calcium ions (Ca²⁺) are crucial for muscle contraction; however they also act as secondary messengers in skeletal muscle and initiate gene transcription that allows adaptation to endurance exercise (Figure1). Repeated muscle contractions during aerobic exercise led to the rise in intracellular calcium, which further activates calcium-sensitive kinases and phosphatases that regulate gene expression and fiber type specification. The key calcium-dependent enzymes involved in muscle adaptation are Ca²⁺/calmodulin-dependent protein kinase (CaMK) and calcineurin (41–43) .

CaMK, particularly CaMKII, is activated by calcium-calmodulin complexes and phosphorylates transcription factors such as CREB, which is involved in mitochondrial biogenesis and oxidative metabolism (41,43). Also, CaMK positively regulates the activity of PGC-1 α , linking calcium signaling to endurance-related adaptations (36).

Calcineurin is a calcium-activated phosphatase that dephosphorylates the NFAT (nuclear factor of activated T cells) family of proteins to regulate gene expression. Calcineurin-NFAT signaling plays a very important role in fiber type specification, facilitating a shift to slow-twitch (type I), oxidative fibers in response to endurance training (44).

The NFAT transcription factors play an important role in determining muscle fiber phenotypes. NFAT proteins are activated by calcineurin and stimulate the expression of the genes associated with oxidative

metabolism and the expression of slow-twitch fibers, including myosin heavy chain I (MyHC-I), and the slow isoforms of both troponin and tropomyosin (6,41,44) .

The interaction between calcineurin-NFAT and other signaling pathways (e.g. mTOR, AMPK) finally determines the overall fiber composition and metabolic profile of the muscle.

Key molecules involved in calcium signaling in skeletal muscles are listed in Table 1.

Inflammation and Stress Response

Intense or prolonged exercise induces transient inflammatory and cellular stress responses in the skeletal muscle (45). Although excessive or chronic inflammation causes negative consequences, the acute inflammatory response to exercise is necessary to initiate muscle remodeling and adaptation (18). The cytokines, redox sensitive signaling pathways, and stress proteins facilitate the adaptation (6) .

The pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), interleukin 1-beta (IL-1 β) and interleukin 6 (IL-6), are released following physical activity, which is subsequently accompanied by the release of anti-inflammatory or regulatory cytokines, including IL-4, IL-10, IL-1RA, and IL-13 (45). TNF- α and IL-1 β activate NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) through the canonical pathway (46). Increased expression of NF- κ B can in addition increase the expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) and heat shock proteins (HSP), promoting recovery and adaptation (47). Exercise induces the expression of HSP70, HSP27, and other chaperones, which help maintain cellular integrity during repeated mechanical and metabolic stress (47). It has been demonstrated that NF- κ B signaling is activated during the strenuous exercise, either in normoxia or acute hypoxia, which includes the increase of p105, p50, IKK α , I κ B β , and glutathione reductase protein levels as well as CaMKII δ D phosphorylation (48).

Maintaining a balance between ROS production and antioxidant defenses is essential for optimal adaptation. Exercise stimulates the production of reactive oxygen species (ROS), particularly from mitochondria and NADPH oxidases (49). Although excessive levels of ROS can harm cellular structures, moderate concentrations function as signaling molecules that facilitate adaptation through NF- κ B, MAPK,

and PGC-1 α signaling (36,49). ROS activate transcription factors such as NRF2, which increases the expression of antioxidant enzymes including SOD, catalase, and GPx (50).

Epigenetic and Transcriptional Regulation

Exercise induces both rapid and massive changes in gene expression in skeletal muscles. Notably, the changes in transcription induced by exercise are time-dependent with initial stress reaction taking place within hours followed by intermediate and late phases characterized by changed expression of genes involved in metabolic regulation and structural remodeling during following days. These dynamic changes are coordinated by the combination of intracellular signaling cascades, epigenetic changes, and non-coding RNA.

Recent meta-analysis by Amar et al. showed that acute and chronic responses to exercise share few genes, highlighting separate molecular signatures for short- and long-term adaptation (51). Immediately after exercise (0–1 h), genes such as hes family bHLH transcription factor 1 (HES1), inhibitor of DNA binding 1 (ID1), SMAD family member 3 (SMAD3), and nuclear receptor subfamily 4 group A member 1 (NR4A1) rise sharply, activating transforming growth factor beta (TGF- β) signaling and metabolic pathways. Angiogenesis genes such as vascular endothelial growth factor A (VEGFA) and platelet-derived growth factor subunit B (PDGFB) indicate stress and hypoxia. At 2–5 h, PPARGC1A (PGC-1 α) peaks, promoting mitochondrial biogenesis and oxidative metabolism, while products of early genes decline. Beyond 20 h, structural remodeling and immune processes dominate, with secreted phosphoprotein 1 (SPP1) upregulated and fatty acid metabolism genes (malonyl-CoA decarboxylase-MLYCD, carnitine palmitoyltransferase 1B-CPT1B) downregulated, reflecting tissue repair and energy shifts. Long-term training triggers expression of genes involved in extracellular matrix synthesis (collagen type IV alpha 1 chain -COL4A1, collagen type IV alpha 2 chain-COL4A2, collagen type I alpha 1 chain-COL1A1) and vascular remodeling (kinase insert domain receptor-KDR, integrin subunit alpha 1-ITGA1). Additionally, exercise modulates ECM turnover through matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), promoting fiber growth and reducing fibrosis risk (52).

Exercise-induced skeletal muscle adaptation is regulated not only by classical signaling pathways but also by epigenetic and non-coding RNA mechanisms that provide dynamic control of gene expression. Histone acetylation in the promoter or the specific genes involved in adaptation to exercise increases, while methylation decreases gene expression (53,54). Additionally, microRNAs (e.g., miR-1, miR-133a, miR-206) regulate muscle growth, regeneration, and metabolic responses, acting on the stability of mRNA (55). Long non-coding RNAs (lncRNAs) such as long non-coding MyoD-associated RNA (lncMyoD) and H19 are involved in satellite cell activation and differentiation, and their expression is modulated by mechanical and metabolic stress (56,57).

Influence of age and sex on skeletal muscle adaptation to exercise

Progressive loss of skeletal muscle mass and function that arises with aging is called sarcopenia. Anabolic resistance, a central feature of sarcopenia, is characterized by reduced muscle protein synthesis in response to resistance exercise and amino acid intake (58). Aging is associated with downregulation of mTORC1 pathway after anabolic stimulation (59). In addition, elevated levels of myostatin in aged adults with excess adiposity and insulin resistance may contribute to sarcopenia (60). Despite these challenges, resistance training remains a potent intervention to counteract sarcopenia. However, older adults may require targeted nutritional strategies, including leucine-enriched protein supplementation to overcome anabolic resistance (58).

Sex-specific factors such as hormonal fluctuations, muscle fiber composition, cardiovascular and metabolic responses influence exercise performance and outcomes. Sex differences in muscle adaptation to exercise are increasingly recognized, driven largely by divergent hormonal profiles in men and women (61). Testosterone promotes muscle hypertrophy through activation of androgen receptors, stimulation of mTORC1 signaling, and enhancement of satellite cell proliferation (62). In contrast, estrogen exerts protective effects on muscle via estrogen receptor α/β (ER α/β), promoting mitochondrial biogenesis, antioxidant defense, and capillary density (63). In women, menstrual cycle phases affect endurance, strength, fatigue, and recovery (64). Personalized programs that account for physiological differences and include targeted strength and flexibility exercises can optimize performance and reduce injury risk.

Discussion

Most molecular studies of exercise adaptation rely on short-term interventions or animal models, limiting their translational relevance. There is a need for longitudinal human studies that track molecular, physiological, and functional changes over extended training periods. Such studies should incorporate repeated biomarker determination, wearable sensor data, and multi-omics profiling. Additionally, the development of in vitro models offers controlled platforms to analyze molecular mechanisms of muscle adaptation.

The identification of reliable biomarkers is critical for monitoring exercise adaptation, guiding training decisions, and preventing over-training. Circulating markers such as creatine kinase (CK), interleukin-6 (IL-6), and C-reactive protein (CRP) provide insights into muscle damage and inflammation. Additionally, changes in myokine and microRNAs levels emerged as promising indicators of muscle remodeling and systemic adaptation.

Recovery status can also be assessed through hormonal markers (e.g., cortisol, testosterone), heart rate variability, and metabolomic signatures. The integration of blood or saliva-based biomarkers data with digital biomarkers determined using wearables enables dynamic monitoring and adjustment of training loads. Future research should focus on validating biomarker panels across diverse populations and exercise modalities, and on developing minimally invasive, cost-effective assays for routine use.

Conclusion

Muscle adaptation to exercise is governed by a complex interplay of molecular pathways that regulate energy metabolism, protein synthesis, mitochondrial biogenesis, and cellular remodeling. Key signaling cascades—including AMPK, mTORC1 and CaMK—coordinate the transcriptional and translational responses necessary for endurance and resistance training adaptations. Transcriptional coactivators such as PGC-1 α and regulators of satellite cell activity play pivotal roles in mediating long-term structural and functional changes in skeletal muscle.

Understanding these molecular mechanisms is essential for optimizing exercise interventions across diverse populations. Age-related anabolic resistance and sex-specific hormonal influences in signaling pathways underscore the need for personalized exercise programs.

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References

1. Battista F, Duregon F, Vecchiato M, Ermolao A, Neunhaeuserer D. Sedentary lifestyle and physical inactivity: A mutual interplay with early and overt frailty. *Nutr Metab Cardiovasc Dis.* 2025; 35(6):103971.
2. Henson J, De Craemer M, Yates T. Sedentary behaviour and disease risk. *BMC Public Health.* 2023; 23(1):2048.
3. Franssen WMA, Nieste I, Verboven K, Eijnde BO. Sedentary behaviour and cardiometabolic health: Integrating the potential underlying molecular health aspects. *Metabolism* 2025; 170: 156320.
4. Safdar A, Hamadeh MJ, Kaczor JJ, Raha S, Debeer J, Tarnopolsky MA. Aberrant mitochondrial homeostasis in the skeletal muscle of sedentary older adults. *PLoS One* 2010; 5(5):e10778.

5. McGee SL, Hargreaves M. Exercise adaptations: molecular mechanisms and potential targets for therapeutic benefit. *Nat Rev Endocrinol* 2020;16(9):495–505.
6. Furrer R, Handschin C. Molecular aspects of the exercise response and training adaptation in skeletal muscle. *Free Radic Biol Med* 2024;223:53–68.
7. Smith JAB, Murach KA, Dyar KA, Zierath JR. Exercise metabolism and adaptation in skeletal muscle. *Nat Rev Mol Cell Biol* 2023;24(9):607–32.
8. Mallett G. The effect of exercise and physical activity on skeletal muscle epigenetics and metabolic adaptations. *Eur J Appl Physiol* 2025;125(3):611–27.
9. Ji F, Lee HS, Kim JH. Resistance exercise and skeletal muscle: protein synthesis, degradation, and controversies. *Eur J Appl Physiol* 2025;125(9).
10. Murach KA, Fry CS, Dupont-Versteegden EE, McCarthy JJ, Peterson CA. Fusion and beyond: Satellite cell contributions to loading-induced skeletal muscle adaptation. *FASEB J* 2021;35(10).
11. Powers SK, Radak Z, Ji LL, Jackson M. Reactive oxygen species promote endurance exercise-induced adaptations in skeletal muscles. *J Sport Health Sci* 2024;13(6):780–92.
12. Beiter T, Zügel M, Hudemann J, Schild M, Fragasso A, Burgstahler C, et al. The Acute, Short-, and Long-Term Effects of Endurance Exercise on Skeletal Muscle Transcriptome Profiles. *Int J Mol Sci* 2024;25(5).
13. Ross M, Kargl CK, Ferguson R, Gavin TP, Hellsten Y. Exercise-induced skeletal muscle angiogenesis: impact of age, sex, angiocrines and cellular mediators. *Eur J Appl Physiol* 2023;123(7):1415.
14. Plotkin DL, Roberts MD, Haun CT, Schoenfeld BJ. Muscle Fiber Type Transitions with Exercise Training: Shifting Perspectives. *Sports* 2021;9(9):127.
15. Wiens L, Losciale JM, Fliss MD, Abercrombie MJ, Darabi D, Li J, et al. Does High-Intensity Interval Training Increase Muscle Strength, Muscle Mass, and Muscle Endurance? A Systematic Review and Meta-Analysis. *Sports* 2025;13(9):293.
16. Thomas ACQ, Stead CA, Burniston JG, Phillips SM. Exercise-specific adaptations in human skeletal muscle: Molecular mechanisms of making muscles fit and mighty. *Free Radic Biol Med* 2024;223:341–56.

17. Iellamo F. Acute responses and chronic adaptations to exercise in humans: a look from the autonomic nervous system window. *J Sports Med Phys Fitness* 2024; 64(2): 137–50.
18. Lambert MI. General Adaptations to Exercise: Acute Versus Chronic and Strength Versus Endurance Training. *Exercise and Human Reproduction: Induced Fertility Disorders and Possible Therapies* 2016; 93–100.
19. Kim DS, Wheeler MT, Ashley EA. The genetics of human performance. *Nat Rev Genet* 2022; 23(1): 40–54.
20. Viecelli C, Ewald CY. The non-modifiable factors age, gender, and genetics influence resistance exercise. *Frontiers in Aging* 2022; 3: 1005848.
21. Jin JB, Robinson A, Soukup T, Black E, Abit A, Hammer SM, et al. Metabolic and molecular regulation in skeletal muscle dysfunction and regeneration. *Front Cell Dev Biol* 2025; 13: 1651553.
22. Lim C, Nunes EA, Currier BS, McLeod JC, Thomas ACO, Phillips SM. An Evidence-Based Narrative Review of Mechanisms of Resistance Exercise-Induced Human Skeletal Muscle Hypertrophy. *Med Sci Sports Exerc* 2022; 54(9): 1546.
23. Ji F, Lee HS, Kim JH. Resistance exercise and skeletal muscle: protein synthesis, degradation, and controversies. *Eur J Appl Physiol* 2025; 125(9): 2353–82.
24. Roberts MD, McCarthy JJ, Hornberger TA, Phillips SM, Mackey AL, Nader GA, et al. Mechanisms of mechanical overload-induced skeletal muscle hypertrophy: current understanding and future directions. *Physiol Rev* 2023; 103(4): 2679-2757.
25. Chen K, Gao P, Li Z, Dai A, Yang M, Chen S, et al. Forkhead Box O Signaling Pathway in Skeletal Muscle Atrophy. *Am J Pathol* 2022; 192(12): 1648–57.
26. Khan MZ, Zugaza JL, Aleman IT. The signaling landscape of insulin-like growth factor 1. *Journal of Biological Chemistry* 2025; 301(1): 108047.
27. Wen Y, Bi P, Liu W, Asakura A, Keller C, Kuang S. Constitutive Notch activation upregulates Pax7 and promotes the self-renewal of skeletal muscle satellite cells. *Mol Cell Biol* 2012; 32(12): 2300–11.

28. Fischer M, Rikeit P, Knaus P, Coirault C. YAP-mediated mechanotransduction in skeletal muscle. *Front Physiol* 2016; 7:174806.
29. Goodman CA, Dietz JM, Jacobs BL, McNally RM, You JS, Hornberger TA. Yes-Associated Protein is up-regulated by mechanical overload and is sufficient to induce skeletal muscle hypertrophy. *FEBS Lett* 2015;589(13):1491–7.
30. Graham ZA, Gallagher PM, Cardozo CP. Focal adhesion kinase and its role in skeletal muscle. *J Muscle Res Cell Motil* 2015; 36(0): 305.
31. Mesquita PHC, Vann CG, Phillips SM, McKendry J, Young KC, Kavazis AN, et al. Skeletal Muscle Ribosome and Mitochondrial Biogenesis in Response to Different Exercise Training Modalities. *Front Physiol* 2021;12:725866.
32. Freitas MC de, Gerosa-Neto J, Zanchi NE, Lira FS, Rossi FE. Role of metabolic stress for enhancing muscle adaptations: Practical applications. *World J Methodol* 2017;7(2): 46.
33. Halling JF, Pilegaard H. PGC-1 α -mediated regulation of mitochondrial function and physiological implications. *Appl Physiol Nutr Metab.* 2020 Sep;45(9):927-936.
34. Steinberg GR, Hardie DG. New insights into activation and function of the AMPK. *Nat Rev Mol Cell Biol* 2023;24(4):255–72.
35. Cantó C, Jiang LQ, Deshmukh AS, Matakı C, Coste A, Lagouge M, et al. Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle. *Cell Metab* 2010;11(3):213.
36. Abu Shelbayeh O, Arroum T, Morris S, Busch KB. PGC-1 α Is a Master Regulator of Mitochondrial Lifecycle and ROS Stress Response. *Antioxidants* 2023;12(5):1075.
37. Juan CG, Matchett KB, Davison GW. A systematic review and meta-analysis of the SIRT1 response to exercise. *Sci Rep* 2023;13(1).
38. Radak Z, Suzuki K, Posa A, Petrovszky Z, Koltai E, Boldogh I. The systemic role of SIRT1 in exercise mediated adaptation. *Redox Biol* 2020;35:101467.
39. Vargas-Ortiz K, Pérez-Vázquez V, Macías-Cervantes MH. Exercise and Sirtuins: A Way to Mitochondrial Health in Skeletal Muscle. *Int J Mol Sci* 2019;20(11):2717.

40. Guan G, Chen Y, Dong Y. Unraveling the AMPK-SIRT1-FOXO Pathway: The In-Depth Analysis and Breakthrough Prospects of Oxidative Stress-Induced Diseases. *Antioxidants* 2025;14(1): 70.
41. Chin ER. The role of calcium and calcium/calmodulin-dependent kinases in skeletal muscle plasticity and mitochondrial biogenesis. *Proc Nutr Soc* 2004;63(2): 279–86.
42. Furrer R, Handschin C. Molecular aspects of the exercise response and training adaptation in skeletal muscle. *Free Radic Biol Med* 2024;223: 53–68.
43. Gehlert S, Bloch W, Suhr F. Ca²⁺-Dependent Regulations and Signaling in Skeletal Muscle: From Electro-Mechanical Coupling to Adaptation. *Int J Mol Sci* 2015;16(1): 1066.
44. Liu W, Chen G, Li F, Tang C, Yin D. Calcineurin-NFAT Signaling and Neurotrophins Control Transformation of Myosin Heavy Chain Isoforms in Rat Soleus Muscle in Response to Aerobic Treadmill Training. *J Sports Sci Med* 2014;13(4): 934-44.
45. Cerqueira É, Marinho DA, Neiva HP, Lourenço O. Inflammatory Effects of High and Moderate Intensity Exercise—A Systematic Review. *Front Physiol* 2020;10: 489354.
46. Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, et al. NF-κB in biology and targeted therapy: new insights and translational implications. *Signal Transduct Target Ther* 2024 ;9(1): 53.
47. Dimauro I, Grazioli E, Lisi V, Guidotti F, Fantini C, Antinozzi C, et al. Systemic Response of Antioxidants, Heat Shock Proteins, and Inflammatory Biomarkers to Short-Lasting Exercise Training in Healthy Male Subjects. *Oxid Med Cell Longev* 2021;2021(1): 1938492.
48. Gallego-Selles A, Galvan-Alvarez V, Martinez-Canton M, Garcia-Gonzalez E, Morales-Alamo D, Santana A, et al. Fast regulation of the NF-κB signalling pathway in human skeletal muscle revealed by high-intensity exercise and ischaemia at exhaustion: Role of oxygenation and metabolite accumulation. *Redox Biol* 2022;55: 102398.
49. Bouviere J, Fortunato RS, Dupuy C, Werneck-De-castro JP, Carvalho DP, Louzada RA. Exercise-Stimulated ROS Sensitive Signaling Pathways in Skeletal Muscle. *Antioxidants* 2021;10(4): 537.
50. Vargas-Mendoza N, Morales-González Á, Madrigal-Santillán EO, Madrigal-Bujaidar E, Álvarez-González I, García-Melo LF, et al. Antioxidant and Adaptative Response Mediated by Nrf2 during Physical Exercise. *Antioxidants* 2019;8(6): 196.

51. Amar D, Lindholm ME, Norrbom J, Wheeler MT, Rivas MA, Ashley EA. Time trajectories in the transcriptomic response to exercise - a meta-analysis. *Nature Communications* 2022;12(1): 3471.
52. Dewi NM, Meiliana A, Defi IR, Amalia R, Sartika CR, Wijaya A, et al. Targeted Therapy for Skeletal Muscle Fibrosis: Regulation of Myostatin, TGF-beta, MMP, and TIMP to Maintain Extracellular Matrix Homeostasis. *Biologics* 2025;19:213–29.
53. Bittel AJ, Chen YW. DNA Methylation in the Adaptive Response to Exercise. *Sports Medicine* 2024;54(6): 1419–58.
54. Hao S, Hu Y, Zhang L, Li J. Histone Acetylation/Deacetylation and Exercise: Epigenetic Mechanisms Underlying Skeletal Muscle Health and Aging. *Epigenetics and Human Health* 2026;15: 95–114.
55. Li H, Liu G, Wang B, Momeni MR. Exosomes and microRNAs as mediators of the exercise. *European Journal of Medical Research* 2025;30(1): 38.
56. Li Y, Zhang Y, Hu Q, Egranov SD, Xing Z, Zhang Z, et al. Functional significance of gain-of-function H19 lncRNA in skeletal muscle differentiation and anti-obesity effects. *Genome Medicine* 2021;13(1): 137.
57. Dong A, Preusch CB, So WK, Lin K, Luan S, Yi R, et al. A long noncoding RNA, lncMyoD, modulates chromatin accessibility to regulate muscle stem cell myogenic lineage progression. *Proc Natl Acad Sci U S A* 2020;117(51):32464–75.
58. Breen L, Phillips SM. Skeletal muscle protein metabolism in the elderly: Interventions to counteract the 'anabolic resistance' of ageing. *Nutrition & Metabolism* 2011;8(1): 68.
59. Francaux M, Demeulder B, Naslain D, Fortin R, Lutz O, Caty G, et al. Aging Reduces the Activation of the mTORC1 Pathway after Resistance Exercise and Protein Intake in Human Skeletal Muscle: Potential Role of REDD1 and Impaired Anabolic Sensitivity. *Nutrients* 2016;8(1): 47.
60. Wilhelmsen A, Stephens FB, Bennett AJ, Karagounis LG, Jones SW, Tsintzas K, et al. Skeletal muscle myostatin mRNA expression is upregulated in aged human adults with excess adiposity but is not associated with insulin resistance and ageing. *GeroScience* 2023;46(2): 2033–49.

61. Landen S, Hiam D, Voisin S, Jacques M, Lamon S, Eynon N. Physiological and molecular sex differences in human skeletal muscle in response to exercise training. *Journal of Physiology* 2023;601(3): 419–34.
62. Basualto-Alarcón C, Jorquera G, Altamirano F, Jaimovich E, Estrada M. Testosterone signals through mTOR and androgen receptor to induce muscle hypertrophy. *Med Sci Sports Exerc* 2013;45(9): 1712–20.
63. Ventura-Clapier R, Piquereau J, Veksler V, Garnier A. Estrogens, Estrogen Receptors Effects on Cardiac and Skeletal Muscle Mitochondria. *Front Endocrinol (Lausanne)* 2019;10: 459867.
64. Ansdell P, Thomas K, Hicks KM, Hunter SK, Howatson G, Goodall S. Physiological sex differences affect the integrative response to exercise: acute and chronic implications. *Exp Physiol* 2020;105(12): 2007–21.

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