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THE ROLE OF MYOGENIC DIFFERENTIATION ABERRATIONS IN THE PHYSICAL PERFORMANCE

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ABSTRACT

Physical performance is influenced by numerous factors, both congenital and non-congenital. Key determinants include diet, physical activity, lifestyle, and environmental exposure. It depends largely on the proper functioning of the musculoskeletal and cardiovascular systems.

Human myogenesis is a tightly regulated process that begins during prenatal development and continues throughout life. The key regulators of this process are myogenic regulatory factors (MRFs), a family of helix–loop–helix transcription factors. These factors cooperate with members of the myocyte enhancer factor 2 (MEF2) family to promote the transcription of muscle-specific genes. In addition, epigenetic mechanisms play a crucial role in regulating gene expression during myogenic differentiation and satellite cell activation. Cell-cycle regulators further contribute to myogenesis by controlling satellite cell proliferation and differentiation, thereby influencing muscle regeneration. Moreover, a wide range of bioactive compounds has been shown to modulate myogenesis through their effects on key regulatory pathways. These regulatory mechanisms may contribute to interindividual variability in physical performance. However, most of the available evidence is derived from in vitro studies, and its relevance to human physiology remains uncertain. Therefore, further research is required to better understand the role of these mechanisms in shaping physical performance. The aim of this review is to summarize current knowledge on the regulatory mechanisms of myogenesis and their role in physical performance. A narrative review of recent literature focusing on molecular and cellular mechanisms regulating myogenesis was conducted.

KEYWORDS

Myoblast Differentiation, Physical Performance, Epigenetics, Cell Cycle, Myogenesis

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1.Introduction

Physical performance among individuals is influenced by numerous congenital and non-congenital factors. One of the most important determinants is environmental exposure and lifestyle, including diet, regular physical activity, and the presence of chronic diseases(Fuentes-Abolafio i in., 2020). Physical performance depends on several physiological systems, including muscular strength and efficiency, cardiac function, and pulmonary capacity(Tieland i in., 2018). These factors may be further modified by daily habits, nutritional status, and well-structured exercise programs. Nevertheless, relatively little is known about genetic factors that directly affect physical performance through modulation of muscle activity and efficiency, particularly in the heart and skeletal muscles(Hsu i in., 2019) (Ghiotto i in., 2022).

Assessment of physical performance requires standardized measurement methods. Consequently, numerous clinical scales and tests have been developed to facilitate the diagnostic process and enable comparison of outcomes across patients. In particular, specialized assessment tools have been designed to evaluate physical performance in individuals with chronic conditions, including rheumatic diseases(Coleman i in., 2020). Such tests should be simple to perform, well tolerated by patients, and easily repeatable.

The fast-paced walk test is one commonly used assessment. This test measures the time required for an individual to walk a predetermined distance. The distance varies depending on the musculoskeletal condition being evaluated and typically ranges from 10 to 80 meters(Unver i in., 2015). Another widely used assessment is the chair stand test, which evaluates the ability to repeatedly stand up from and sit down on a chair. The test may be performed in a time-based format, in which the individual completes as many repetitions as possible within a specified time, or in a repetition-based format, where the individual is instructed to complete a set number of repetitions in the shortest possible time(Dobson i in., 2013) (Bohannon, 2006).

The stair climb test measures the time required for an individual to ascend and/or descend a predetermined number of stairs. The number of stairs included in the test depends on the patient's clinical condition(Iijima i in.,

2019). Walking endurance can be evaluated using walk tests that measure the distance covered within a specified time interval. Depending on the clinical context, walk tests lasting 2, 6, or 12 minutes are commonly used(Balke, 1963) (McGavin i in., 1976) (Butland i in., 1982). Another frequently applied assessment is the Timed Up and Go (TUG) test, which evaluates not only physical performance but also balance and agility. During the test, the individual is instructed to stand up from a chair, walk 3 meters, turn 180°, return to the chair, and sit down. The total time required to complete these tasks is recorded(Yuksel i in., 2017).

In addition to clinical assessments used in patients, numerous tests have been developed to evaluate musculoskeletal performance in athletes. These assessments, often referred to as performance-based tests, measure physical function in relation to the specific demands of different sports disciplines(Barbosa i in., 2024). Examples include the Medicine Ball Explosive Power Test used in volleyball players, the One-Arm Hop Test used in wrestlers, the Arm-Jump Board Test applied in rock climbers, and the Closed Kinetic Chain Upper Extremity Stability Test, which can be utilized across multiple sports. These tests may evaluate the time required to complete a task, the number of repetitions performed within a given time, or the duration for which a task can be maintained(Stockbrugger & Haennel, 2001) (Falsone i in., 2002) (Laffaye i in., 2014) (Popchak i in., 2021).

Human myogenesis is a tightly regulated process that begins during prenatal development. During early embryogenesis, the paraxial mesoderm forms somites that subsequently differentiate into dermatomyotomes. From these structures, the myotome arises and gives rise to myogenic progenitor cells. These progenitors differentiate into myoblasts that proliferate, migrate, and fuse to form multinucleated myofibers(Kahane i in., 2002). After birth, a subset of these myogenic cells persists as satellite cells, which remain in a quiescent state and serve as a key source of muscle regeneration and repair throughout life(Yin i in., 2013).

The regulation of myogenesis involves a complex network of genetic and epigenetic mechanisms that coordinate muscle development and regeneration(Wu & Yue, 2024). Among the key regulators are the myogenic regulatory factors (MRFs), a family of basic helix–loop–helix transcription factors, including Myf5, MyoD, Myogenin, and MRF4, that control the specification and differentiation of the myogenic lineage(Asfour i in., 2018) (Zammit, 2017). Myogenesis is also regulated by members of the myocyte enhancer factor 2 (MEF2) family, which interact with MRFs to promote the transcription of muscle-specific genes(Brand, 1997). In addition, epigenetic mechanisms such as histone modifications and chromatin remodeling influence gene expression during myogenic differentiation and satellite cell activation(Massenet i in., 2021). These processes are further coordinated by multiple signaling pathways, including Notch, Hedgehog, fibroblast growth factor (FGF), epidermal growth factor (EGF), and bone morphogenetic protein (BMP), which regulate the balance between proliferation and differentiation of myogenic precursors(Perrimon i in., 2012) (Ling i in., 2021).

Given the fundamental role of skeletal muscle in movement, strength generation, and endurance, alterations in these regulatory pathways may ultimately influence muscle structure and function. Consequently, genetic and epigenetic factors affecting myogenesis may contribute to interindividual differences in muscle performance and physical capacity.

In this review, we aim to summarize current knowledge regarding abnormalities in the aforementioned regulatory mechanisms of myogenesis and discuss their potential implications for physical performance.

2.1 Myogenic regulatory factors

Over the past decades, extensive research has led to the identification of key regulators of muscle development known as myogenic regulatory factors (MRFs). These proteins belong to a family of helix–loop–helix transcription factors that play critical roles in the specification, differentiation, and maintenance of the myogenic lineage, including the regulation of muscle satellite cells(Asfour i in., 2018). The MRF family comprises Myf5, MyoD, myogenin, and MRF4. Although these factors can function independently, they also exhibit overlapping and complementary roles in orchestrating myoblast differentiation during both prenatal development and postnatal muscle regeneration(Zammit, 2017).

Numerous modulators of this regulatory pathway have been identified(Bagherniya i in., 2022). Among them, bioactive compounds derived from green tea exhibit a range of beneficial properties, including anti-inflammatory, antihypertensive, insulin-sensitizing, and antioxidant effects(H. M. Kim & Kim, 2013). Epicatechin treatment in mice has been shown to increase MyoD activity and promote myogenic conversion as well as fibroblast differentiation(Lee i in., 2017). Furthermore, tannase-converted green tea extract significantly upregulated the expression of *myogenin*, *Myf5*, and *MyoD* in C2C12 skeletal muscle cells, suggesting its potential application in the treatment of sarcopenia(Hong i in., 2020). In humans, the administration of catechins in combination with exercise resulted in a statistically significant improvement in physical function in women with sarcopenia, including enhanced walking ability and increased muscle mass(H. Kim i in., 2013).

3-(4-hydroxy-3-methoxyphenyl)propionic acid (HMPA), also known as dihydroferulic acid, is a compound found in various fermented foods and is characterized by notable anti-inflammatory and antioxidant properties(Tian i in., 2022). Low-dose administration of HMPA in mice increased *Myf5* expression, suggesting a potential role in promoting muscle development. Additionally, HMPA-treated groups exhibited enhanced grip strength(Tong i in., 2024).

Tetracycline, a widely used antibiotic, has also been implicated in muscle regeneration. Combined with endurance exercise, tetracycline treatment was shown to enhance recovery following muscle atrophy, such as that induced by prolonged limb immobilization, potentially through upregulation of *MRF* expression(Shefer i in., 2008).

Umbelliferone, a derivative of coumarin, has been associated with various biological activities(Hijazin i in., 2019). In C2C12 myoblasts exposed to high-glucose conditions, umbelliferone treatment significantly increased the expression of *MyoD*, *myogenin*, and *myosin*, thereby promoting myoblast differentiation. These findings suggest its therapeutic potential in mitigating diabetes-related muscle atrophy(D. Y. Kim i in., 2025).

Myostatin is a key growth and differentiation factor that acts as a primary negative regulator of skeletal muscle development(Beyer i in., 2013). Its signaling has been shown to suppress the transcription of *MyoD* and *Myf5*, thereby reducing cell proliferation and myoblast differentiation(Amthor i in., 2002). Notably, CRISPR/Cas9-mediated knockdown of myostatin in C2C12 cells resulted in increased expression of *MyoD* and myogenin, indicating that this approach may represent a promising therapeutic strategy for restoring muscle mass and enhancing the regenerative capacity of muscle stem cells(Elashry i in., 2025).

Purple perilla (*Perilla frutescens*), a herb widely cultivated in Asia, has also demonstrated potential in this context. Peptides isolated from purple perilla seeds and administered in mice led to increased expression of *MyoD* and *myogenin*, as well as enhanced muscle fiber thickness. These results suggest that purple perilla seed peptides may effectively promote muscle growth and improve exercise tolerance(Liu i in., 2020).

2.2 Myocyte Enhancer Factor 2

The myocyte enhancer factor 2 (MEF2) family of transcription factors plays a crucial role in the regulation of myogenesis and muscle morphogenesis. MEF2 proteins interact with myogenic regulatory factors (MRFs) through complex protein–protein interactions, thereby enhancing the transcriptional activation of muscle-specific genes required for muscle fiber formation and maturation(Brand, 1997). Compared with MRFs, MEF2 transcription factors exhibit broader biological functions and pleiotropic activity, as they are also involved in the regulation of other developmental processes, including neurogenesis and osteogenesis(Heidenreich & Linseman, 2004) (Blixt i in., 2020). The coordinated activity of MRFs and MEF2 proteins therefore constitutes a key regulatory axis ensuring proper activation of the muscle-specific transcriptional program.

Despite their importance, relatively little is known about factors that specifically regulate *MEF2* expression and their impact on physical performance. *MEF2* activity is known to be modulated by class II histone deacetylases (HDACs), which act as transcriptional repressors. Experimental studies in mice have demonstrated that repression of *MEF2* activity via HDACs suppresses the formation of slow-twitch muscle fibers, whereas enhanced *MEF2* activity promotes their development and is associated with increased running endurance compared to wild-type controls(Potthoff i in., 2007).

Further insights into *MEF2* regulation have emerged from studies in patients with chronic obstructive pulmonary disease (COPD). Calcineurin, a calcium-dependent phosphatase, plays a key role in activating type I (slow-twitch) muscle fiber gene expression(Long & Zierath, 2008). It has been shown to stimulate *MEF2* transcriptional activity, thereby promoting the expression of genes associated with oxidative muscle fibers(Chin i in., 1998). Although these mechanisms have been investigated in the context of reduced muscle endurance in COPD patients, the available data remain inconclusive and do not fully explain the underlying molecular basis of impaired physical performance, highlighting the need for further research(Natanek i in., 2013).

Myocilin (Myoc) is a protein involved in maintaining muscle cell membrane integrity. In mouse models, downregulation of *Myoc* leads to muscle wasting, whereas its overexpression results in increased skeletal muscle mass. Although the precise relationship between *Myoc* expression and muscle mass regulation was previously unclear, recent findings indicate that MEF2 functions as an upstream activator of *Myoc* transcription, providing new insight into the regulatory mechanisms governing muscle maintenance(Joe i in., 2012) (Judge i in., 2020).

2.3 Epigenetic regulators

Epigenetic mechanisms further contribute to the regulation of myogenesis by modulating chromatin accessibility and gene expression without altering the underlying DNA sequence. These mechanisms include post-translational histone modifications, DNA methylation, and chromatin remodeling, which collectively regulate the transcriptional activity of genes involved in myogenic differentiation(Massenet i in., 2021). Epigenetic regulation is particularly important for controlling the activation, proliferation, and differentiation of satellite cells during muscle repair and regeneration. Through dynamic changes in chromatin structure, epigenetic regulators coordinate the transition of satellite cells from a quiescent state to active proliferation and subsequent differentiation into mature muscle cells.

Myoblast differentiation is governed by a complex epigenetic landscape that operates in concert with canonical myogenic transcription factors, including MyoD, myogenin, and Pax7. DNA methylation constitutes a central regulatory mechanism; during myogenic differentiation, promoters of key myogenic genes (*MYOD1*, *MYOG*) undergo active demethylation mediated by ten–eleven translocation (TET) enzymes (TET1, TET2), resulting in transcriptional activation(Yang i in., 2022) (Zhong i in., 2017). In the context of physical performance, such mechanisms facilitate accelerated muscle regeneration, metabolic adaptation, and the establishment of long-term epigenetic memory, thereby enhancing subsequent adaptive responses to training stimuli(Kanzleiter i in., 2015). DNA methylation patterns are dynamically remodelled in response to both acute and chronic exercise, particularly within enhancer regions, gene bodies, and intergenic domains(Bittel & Chen, 2024).

Histone modifications are of comparable importance. Myogenic differentiation is associated with widespread transcriptional repression, characterised by reduced histone acetylation and enrichment of repressive histone marks(Sincennes i in., 2016). These chromatin alterations enable tightly regulated activation of exercise-responsive genes, govern muscle fibre-type transitions, modulate energy metabolism, and provide a molecular substrate for sustained training adaptations(Lim i in., 2020).

The concept of skeletal muscle “epigenetic memory” has emerged as a key paradigm; selected genes (*FLNB*, *MYH9*, *SRGAP1*, *SRGN*, *ZMIZ1*) display persistent hypomethylation even during periods of detraining, despite reversion of muscle mass to baseline levels(Turner i in., 2019). This phenomenon may underlie the accelerated reacquisition of muscle function following training cessation.

Reactive oxygen species (ROS), generated during exercise, contribute to epigenomic remodelling through both direct and indirect mechanisms. Oxidative modification of guanine to 8-oxoguanine functions as an epigenetic signal and may influence promoter and enhancer methylation profiles(Radak i in., 2024) (Caporossi & Dimauro, 2024). Notably, higher physical fitness is associated with a deceleration of the DNA methylation-based ageing clock(Radak i in., 2024).

Exercise-induced epigenetic modifications target genes implicated in energy homeostasis, mitochondrial function, muscle regeneration, and calcium signalling pathways(Caporossi & Dimauro, 2024) (Mallett, 2025) (Widmann i in., 2019). Emerging evidence indicates that such epigenetic signatures may serve as clinically relevant biomarkers for the development of personalised training interventions(Widmann i in., 2019).

2.4 Cell cycle regulators

Cell proliferation and differentiation are controlled by cell-cycle regulators. The regulation of the cell cycle is complex and involves multiple signaling pathways, including Notch, Hedgehog, fibroblast growth factor (FGF), epidermal growth factor (EGF), and bone morphogenetic protein (BMP) pathways. These signaling cascades coordinate cell-cycle progression and determine whether cells undergo mitosis or differentiation. Disruptions in these pathways may impair myoblast proliferation and differentiation(D. Y. Kim i in., 2025) (Beyer i in., 2013).

Cell-cycle regulators influence physical performance through the control of satellite cell proliferation and differentiation, regulation of muscle fibre phenotype, and modulation of metabolic adaptations to exercise. Key mediators, including CDK1, cyclin D3, the CDK4–E2F3 axis, and cyclin-dependent kinase inhibitors (p21 and p27), play critical roles in determining both the regenerative capacity of skeletal muscle and its functional properties.

Cyclin D3 deficiency has been shown to induce a shift in muscle fibre phenotype towards an oxidative profile, accompanied by enhanced endurance performance and hypermetabolism(Giannattasio i in., 2018). Cyclin D3–deficient mice exhibit an increased proportion of highly oxidative fibres within fast-twitch muscle groups, which are physiologically characterised by predominantly glycolytic metabolism(Giannattasio i in., 2018). This phenotypic remodelling towards a slower, oxidative profile is associated with increased energy expenditure and

augmented fatty acid oxidation. These findings indicate that cyclin D3 contributes to the regulation of muscle fibre phenotype and, indirectly, to whole-body metabolic homeostasis(Giannattasio i in., 2018).

The CDK4–E2F3 signalling axis plays a pivotal role in the regulation of myogenesis and skeletal muscle metabolism, promoting both the abundance and functional capacity of oxidative fibres(Bahn i in., 2023). Mice expressing constitutively active *Cdk4*, incapable of binding its inhibitor p16INK4a, are protected against obesity and diabetes, and their skeletal muscles display an increased oxidative fibre content, enhanced mitochondrial function, and elevated glucose uptake(Bahn i in., 2023). Conversely, loss of *Cdk4* or skeletal muscle-specific deletion of *E2F3* results in reduced oxidative fibre content, impaired mitochondrial function, diminished exercise capacity, and increased susceptibility to metabolic dysfunction(Bahn i in., 2023).

CDK1 is essential for satellite cell proliferation, muscle regeneration, and overload-induced hypertrophy of muscle fibres(Kobayashi i in., 2020). *Cdk1* is highly expressed in myoblasts and is downregulated during myogenic differentiation(Kobayashi i in., 2020). Deletion of *Cdk1* in satellite cells leads to impaired muscle regeneration following injury, attributable to reduced in vivo proliferative capacity of these cells(Kobayashi i in., 2020). Furthermore, *Cdk1* expression in satellite cells is required for the development of overload-induced muscle fibre hypertrophy(Kobayashi i in., 2020).

Physical activity modulates the expression of cyclin-dependent kinase inhibitors, such as *p21* and *p27*, thereby influencing satellite cell activation(Roberts i in., 2010). Gene expression analyses of cell-cycle regulators provide evidence that satellite cell activation and proliferation may occur at early time points following exercise, including after resistance training(Roberts i in., 2010). In studies involving older women, resistance training was associated with a reduction in p27Kip1 levels, suggesting that mechanical loading may partially overcome its inhibitory effects on cell-cycle progression(Bamman i in., 2004).

Endurance training affects satellite cell function through mechanisms linked to metabolic reprogramming. It has been shown to promote self-renewal capacity while restraining differentiation, partly through reduced mitochondrial oxygen consumption under resting conditions(Abreu & Kowaltowski, 2020). Skeletal muscles from endurance-trained animals exhibit enhanced regenerative capacity following injury, as evidenced by increased density of newly formed fibres, reduced inflammation, and attenuated fibrosis(Abreu & Kowaltowski, 2020). These effects are associated with metabolic alterations in satellite cells and the maintenance of their progenitor properties(Abreu & Kowaltowski, 2020).

Understanding the role of cell-cycle regulators in shaping physical performance has important implications for the pathophysiology and treatment of muscle disorders, including sarcopenia and muscular dystrophies. Modulation of CDK, cyclin, and cyclin-dependent kinase inhibitor activity may represent a potential therapeutic strategy to enhance muscle regeneration, improve exercise capacity, and prevent age- or disease-related depletion of the satellite cell pool.

3. Discussion

The present body of literature highlights the complexity of regulatory mechanisms governing myoblast differentiation and their impact on physical performance. Although substantial progress has been made in identifying key molecular pathways, important gaps remain in understanding how these regulatory systems interact and translate into functional outcomes across different physiological and pathological conditions.

Myogenic regulatory factors (MRFs) represent the core transcriptional machinery driving myogenesis and remain the most extensively characterized components of this process. Their role in coordinating myoblast specification, differentiation, and regeneration provides a well-established foundation for studying muscle development. However, as demonstrated by the studies discussed, MRF activity is not independent but instead operates within a broader regulatory network. In particular, interactions with MEF2 transcription factors significantly enhance the transcriptional activation of muscle-specific genes, underscoring the importance of cooperative regulation in achieving efficient muscle fiber formation and maturation(Brand, 1997) (Heidenreich & Linseman, 2004) (Blixt i in., 2020).

Beyond transcription factor networks, epigenetic regulation emerges as a critical layer of control that enables dynamic and reversible modulation of gene expression in response to environmental stimuli. Mechanisms such as DNA methylation, histone modifications, and chromatin remodeling not only regulate myogenic gene activation but also contribute to long-term adaptations associated with physical activity(Kanzleiter i in., 2015). The concept of skeletal muscle “epigenetic memory” provides a compelling explanation for the enhanced responsiveness to repeated training stimuli, suggesting that prior exercise exposure induces persistent molecular changes that facilitate subsequent muscle adaptation(Turner i in., 2019).

Cell-cycle regulators further integrate proliferative and differentiation signals, ensuring proper expansion of the satellite cell pool and efficient muscle regeneration. Key regulators, including CDK1, cyclin D3, and the CDK4–E2F3 axis, have been shown to influence not only myoblast proliferation but also muscle fiber-type composition and metabolic properties. These findings highlight a critical link between cell-cycle control and functional muscle performance, particularly in the context of endurance capacity and metabolic health(Giannattasio i in., 2018) (Bahn i in., 2023).

Importantly, a wide range of external modulators, including bioactive compounds, exercise, and metabolic signals have been shown to influence these regulatory pathways at multiple levels. Compounds such as catechins, epicatechin, and other plant-derived molecules demonstrate the capacity to modulate MRF expression and promote myogenic differentiation, while exercise-induced signaling affects epigenetic and cell-cycle mechanisms that underpin muscle adaptation. These observations suggest considerable potential for the development of targeted therapeutic and lifestyle-based interventions aimed at improving muscle function(Hong i in., 2020) (H. Kim i in., 2013) (D. Y. Kim i in., 2025) (Liu i in., 2020).

4. Conclusions

Myoblast differentiation and its contribution to physical performance are regulated by a complex, multilayered network involving transcription factors, epigenetic mechanisms, and cell-cycle regulators. While MRFs and MEF2 proteins form the central framework of myogenic control, additional regulatory layers provide the flexibility required for precise adaptation to physiological demands.

Emerging evidence demonstrates that these pathways can be modulated by external factors such as exercise and bioactive compounds, highlighting their potential as targets for therapeutic intervention. Despite these advances, several limitations remain. Much of the available evidence is derived from in vitro systems or animal models, which may not fully recapitulate human physiology. Additionally, variability in experimental design, intervention protocols, and outcome measures complicates direct comparison across studies. The molecular mechanisms linking these regulatory pathways to measurable improvements in physical performance also remain incompletely defined.

Future research should focus on integrative approaches that combine molecular, physiological, and clinical data to better understand the interplay between transcriptional, epigenetic, and cell-cycle regulation. In particular, well-designed human studies are needed to validate preclinical findings and to explore the translational potential of targeting these pathways in the prevention and treatment of muscle-related disorders.

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