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REVIEW

Emerging roles of epigenetics in the pathogenesis of sarcopenia

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ABSTRACT

Sarcopenia is an age-associated degenerative disorder of skeletal muscle, characterized by the progressive decline in muscle mass and function, which increases the risk of falls, injuries, and accidental death in older adults. Deciphering its pathogenic mechanisms is crucial for advancing early detection, precision prevention, and ultimately improving the quality of life for the elderly population. Increasing evidence suggests that epigenetic regulation plays a central role in driving sarcopenia. DNA methylation, chromatin remodeling, and noncoding RNA regulation collectively accelerate the deterioration of bone and muscle by altering gene expression involved in biosynthesis and metabolism, disrupting protein homeostasis, activating inflammatory pathways, and compromising mitochondrial integrity. This review, which synthesizes the most recent progress in epigenetic research on sarcopenia, uses structured searches of PubMed and Web of Science for studies published from 2014 to the present and emphasizes how these interconnected regulatory networks drive the initiation and progression of the disease. Importantly, we emphasize their translational potential to identify novel biomarkers, enabling early risk stratification and informing the development of targeted therapeutic strategies, thereby laying the groundwork for precision clinical intervention.

PLAIN LANGUAGE SUMMARY

Sarcopenia is a condition in which older adults gradually lose muscle mass and strength, making everyday activities harder and increasing the risk of falls and disability. Recent research indicates that this process is not only related to aging or lifestyle, but also to "epigenetic changes" – molecular switches that control how genes function without altering the DNA itself.

These epigenetic switches can affect how muscle cells grow, repair damage, produce energy, and respond to inflammation. When these switches become disrupted with age, they can speed up muscle loss. This review summarizes the latest findings on three major types of epigenetic changes: DNA methylation, chromatin remodeling, and noncoding RNAs. Together, these mechanisms influence muscle regeneration, energy metabolism, and protein balance, which may explain why muscle and bone often deteriorate simultaneously.

Because epigenetic changes are reversible, they offer promising opportunities for early diagnosis and the development of new treatments. Blood-based biomarkers, targeted drugs, RNA therapies, and gene-editing tools are emerging as potential strategies to slow or reverse muscle decline. Understanding these mechanisms may lead to earlier detection and more personalized approaches to prevent sarcopenia, helping older adults maintain strength and independence.

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1. Introduction

Sarcopenia is a complex clinical disorder whose prevalence increases progressively with age, making aging the most significant risk factor [1]. Most patients with sarcopenia present with marked reductions in skeletal muscle mass, decreased muscle strength, and impaired physical performance, leading to fatigue, slow gait, impaired balance, reduced grip strength, and a higher risk of falls and fractures [2]. Moreover, as skeletal muscle is a primary site of glucose uptake and energy metabolism, its decline and dysfunction further increase the risk of diabetes, obesity, atherosclerosis, and cardiovascular disease [3–5]. These adverse outcomes ultimately compromise overall health and quality of life in the elderly. Epidemiological data indicate that among individuals aged 45 years and older, the prevalence of suspected sarcopenia is approximately 22.91%, with confirmed cases accounting for 14.11% [6]. A thorough understanding of the underlying mechanisms of sarcopenia is therefore crucial for its prevention,

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Article highlights

- This review provides an updated synthesis of epigenetic mechanisms driving osteosarcopenia, focusing on DNA methylation, chromatin remodeling, and noncoding RNA – mediated regulation.
- Age-related chronic inflammation, oxidative stress, and metabolic imbalance collectively induce epigenetic alterations that impair osteogenic differentiation and compromise muscle regenerative capacity.
- Aberrant DNA methylation of key regulatory genes – including *RUNX2, SPARC, OPG, MYOD1*, and PGC-1α—disrupts bone remodeling processes and accelerates skeletal muscle metabolic decline.
- Dysregulated histone deacetylase (HDAC) activity and reduced *SIRT1/SIRT3* function amplify cellular senescence, weaken antioxidant defense pathways, and promote degenerative changes in both bone and muscle tissues.
- Alterations in noncoding RNA networks, particularly miR-29b, miR-128, and miR-21, contribute to the coordinated deterioration of bone and muscle by modulating *IGF*-1/*SIRT*1 signaling, osteoclast activation, and muscle fibrosis.
- Elucidating these epigenetic regulatory pathways offers new mechanistic insights and provides a scientific basis for developing integrated prevention and therapeutic strategies for osteosarcopenia.

early detection, and targeted treatment. Over the past decade, significant progress has been made in identifying the key contributors to sarcopenia, including imbalances in protein synthesis and degradation, mitochondrial dysfunction, and disturbances in neuroendocrine regulation [7]. Moreover, growing evidence suggests that bone and muscle are not independent structures. Instead, they form a tightly interconnected "bone – muscle" network. This network is linked through mechanical loading and metabolic signaling [8]. Chronic inflammation, hormonal alterations, and metabolic dysregulation can disrupt its stability. As a result, bone loss and muscle decline may follow a highly synchronized pathological trajectory [9]. Elucidating the molecular interactions between bone and muscle is essential. It can help uncover the biological basis underlying the co-occurrence of sarcopenia and osteoporosis. It can also provide a theoretical foundation for developing integrated prevention and treatment strategies.

Epigenetics, the study of heritable modifications in gene expression that occur without changes to the DNA sequence, has emerged as a powerful approach for uncovering aging-related molecular mechanisms and elucidating the complex regulatory networks associated with sarcopenia. The principal epigenetic mechanisms include DNA methylation, chromatin remodeling, histone modifications, and noncoding RNAs (ncRNAs)-mediated regulation, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) [10,11]. As research continues to advance, it has become increasingly recognized that epigenetic mechanisms play a central role in the pathogenesis of sarcopenia, particularly DNA methylation and noncoding RNA-mediated regulation. These mechanisms alter gene expression patterns and chromatin architecture, thereby impairing cellular function and tissue homeostasis, ultimately leading to skeletal muscle degeneration. Thus, epigenetic studies not only deepen our understanding of the molecular pathology of sarcopenia but also provide a theoretical basis for its early detection and targeted intervention.

In this review, we conducted structured searches in PubMed and Web of Science using key terms related to sarcopenia, skeletal muscle aging, osteosarcopenia, epigenetics, DNA methylation, chromatin remodeling, and noncoding RNAs. The search focused on peer-reviewed studies published from 2014 to the present, a period marked by rapid advances in epigenomic technologies and their application to muscle biology. We included English-language studies that investigated molecular mechanisms, epigenetic alterations, or regulatory networks implicated in muscle atrophy, with priority given to population-based research. Articles lacking relevance to skeletal muscle pathophysiology or epigenetic regulation, as well as non-peer-reviewed material, were excluded. By integrating evidence across DNA methylation, chromatin remodeling, and ncRNA-mediated pathways, this review aims to provide a comprehensive framework for understanding the epigenetic drivers of sarcopenia and to highlight their significance for biomarker development and targeted therapeutic innovation.

2. Epigenetic mechanisms of osteosarcopenia

Sarcopenia is increasingly recognized as a shared phenotype linking osteoporosis and age-related muscle wasting. Its development reflects not merely the degeneration of a single tissue but a systemic imbalance within the bone – muscle functional unit in the aging milieu. Recent studies have revealed that, beyond mechanical loading, a complex endocrine and metabolic interaction network exists between bone and skeletal muscle [12]. Within this framework, epigenetic regulation serves as a crucial molecular bridge linking inflammation, metabolic dysregulation, and tissue functional decline. Age-related functional decline induces widespread epigenetic alterations in bone and skeletal muscle cells, including aberrant DNA methylation, dysregulated histone modifications, and remodeling of non-coding RNA expression profiles. These alterations affect cellular differentiation, energy metabolism, and tissue regenerative capacity, collectively driving bone loss and muscle atrophy [13].

In bone tissue, reduced mesenchymal stem cell differentiation into osteoblasts is closely associated with promoter methylation of key osteogenic genes. Hypermethylation of promoter regions in crucial osteogenic genes, such as Runx-related transcription factor 2 (*RUNX2*) and secreted protein acidic and rich in cysteine (*SPARC*), impairs mesenchymal stem cell (MSC) differentiation toward the osteogenic lineage, while increased methylation of osteoprotegerin (OPG) disrupts the receptor activator of nuclear factor-κB ligand (RANKL)/OPG balance, thereby enhancing osteoclast activity and accelerating bone resorption [14,15]. Concurrently, excessive activation of histone deacetylases (HDACs) suppresses transcription of osteogenic genes, promoting preferential differentiation of mesenchymal stem cells into adipocytes rather than osteoblasts, and also inhibits myoblast determination protein 1 (*MyoD*), thereby impairing satellite cell activation and subsequent myofibrillar regeneration [16]. Similarly, in skeletal muscle, age-related epigenetic drift affects the stability of the bone – muscle functional unit. Dynamic changes in DNA methylation and histone modifications regulate Myogenin-mediated terminal myoblast differentiation and myofibrillar formation – thereby determining muscle mass and mechanical output – and also govern

peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) – mediated mitochondrial biogenesis, myofibrillar metabolic phenotypes, and anti-inflammatory responses, ultimately shaping muscle function. Disruption of this epigenetic equilibrium impairs muscle differentiation and reduces metabolic capacity, leading to declines in muscle strength and endurance. This reduces mechanical stimulation of bone and weakens the positive regulation of osteogenesis and bone remodeling by myokines (e.g., irisin), ultimately disrupting muscle – bone homeostasis and promoting the progression of sarcopenia and osteoporosis [17,18].

Notably, endocrine interactions between bone and muscle may facilitate cross-tissue regulation through epigenetic mechanisms. Bone-derived factors, such as osteocalcin and osteonectin, have been shown to influence skeletal muscle metabolic function and insulin sensitivity [19]. Although direct evidence is lacking that osteogenic factors induce DNA methylation or chromatin structural changes in myocytes, their potential to indirectly influence epigenetic enzyme activity via inflammatory and metabolic signaling pathways is biologically plausible. Conversely, skeletal muscle, as an endocrine organ, also participates in bone remodeling regulation by secreting myokines. For example, myostatin not only inhibits muscle growth but is also believed to suppress osteogenic differentiation, while factors such as insulin-like growth factor 1 (*IGF-1*) and irisin promote bone formation [20]. Under chronic inflammation or sarcopenic conditions, persistently elevated pro-inflammatory myokines may enhance DNA methyltransferase or histone deacetylase activity, thereby suppressing osteogenic gene expression and promoting bone resorption. Furthermore, muscle-derived exosomes and their cargo microRNAs are considered potential cross-tissue information carriers involved in the epigenetic regulation of osteocyte gene expression [21]. However, direct evidence for such cross-tissue epigenetic regulation in human sarcopenia remains limited.

Current research on bone – muscle epigenetic interactions remains exploratory mainly. Existing evidence primarily derives from animal models and in vitro experiments, with most studies focusing on single tissues. The difficulty in obtaining paired human bone and skeletal muscle samples, coupled with the challenges of longitudinal follow-up, hampers the establishment of clear cross-tissue causal relationships. Furthermore, systemic variables such as inflammation status, physical activity, and nutritional factors may confound epigenetic analyses. Therefore, future studies should integrate single-cell epigenomics, multi-omics approaches, and longitudinal cohort designs to elucidate bone – muscle epigenetic regulatory networks systematically.

3. Roles of DNA methylation in sarcopenia

DNA methylation is an essential epigenetic process that governs muscle growth, differentiation, and metabolic activity by regulating the expression of genes associated with muscle physiology, thereby contributing to the onset of sarcopenia. Evidence suggests that age-related alterations occur in skeletal muscle methylation patterns, with younger individuals typically exhibiting higher methylation levels than older individuals. In contrast, reduced methylation is frequently observed in aged muscle, a phenomenon linked to decreases in muscle mass and functional capacity. Notably, reactive oxygen species (ROS) can induce DNA damage and alter methylation patterns. Together with inflammatory responses, these processes are key pathological mechanisms in sarcopenia, and abnormal DNA methylation may further exacerbate them [22]. Moreover, increasing attention has been directed toward active DNA demethylation processes and their contribution to muscle aging. Recent studies emphasize the critical role of the ten – eleven translocation (*TET*) enzymes, which are involved in skeletal muscle development and the regulation of aging-associated adaptations [23].

3.1. DNA methylation and its regulatory machinery

DNA methylation represents a fundamental epigenetic modification carried out by DNA methyltransferases (*DNMTs*), which catalyze the transfer of methyl groups from S-adenosylmethionine (SAM) to cytosine bases, thereby producing 5-methylcytosine (5-mC) and influencing transcriptional regulation [24]. This epigenetic mechanism plays a crucial role in safeguarding genomic integrity, facilitating cell differentiation, and regulating age-related physiological processes [25]. As individuals age, significant alterations in DNA methylation occur, characterized primarily by a global decrease in DNA methylation and hyper- or hypomethylation in specific genomic regions [26]. For example, differential methylation within the promoters or enhancers of sarcopenia-related genes (e.g., *GAB2*, *JPH3*, and *HLA-DQB1*) can disrupt key signaling pathways in myocytes. These pathways include *IGF-1*/phosphatidylinositol 3-kinase (PI3K)-protein kinase B(AKT) signaling, mitochondrial energy metabolism, and myocyte adhesion and regeneration signaling pathways (such as the Notch and Rap pathways). This disruption may reduce muscle protein synthesis and accelerate protein degradation. It can also promote myofiber atrophy, thereby contributing to sarcopenia [27]. Furthermore, aberrant methylation events have been strongly linked to age-related loss of muscle mass and declines in functional performance [28].

To elucidate the role of DNA methylation in regulating skeletal muscle physiology, researchers have developed a skeletal muscle-specific DNA methyltransferase 3a (*Dnmt3a*) transgenic mouse model [29]. In this model, *Dnmt3a* overexpression increases DNA methylation in skeletal muscle, mimicking age-related methylation accumulation. Comprehensive assessments revealed that mice overexpressing *Dnmt3a* exhibited a distinct muscle atrophy phenotype characterized by decreased muscle mass, reduced strength, a transition from fast-twitch to slow-twitch fibers, and impaired metabolic adaptability. These results suggest that DNA methylation plays a significant role in skeletal muscle degeneration, offering insights into the molecular mechanisms underlying muscle aging.

Aging is characterized by persistent oxidative stress and chronic low-grade inflammation, both of which closely interact with DNA methylation machinery [30,31]. Excessive *ROS* can alter DNMT activity and induce locus-specific hyper- or

hypomethylation, thereby reshaping transcriptional programs associated with myogenesis and mitochondrial metabolism [32]. Simultaneously, pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) modulate methylation-related enzymes and influence promoter methylation patterns of key muscle regulatory genes, including *MyoD* and *IGF-1* [23]. Importantly, aberrant methylation of mitochondrial and metabolic genes may further exacerbate mitochondrial dysfunction, enhance *ROS* generation, and sustain inflammatory signaling [33]. Therefore, oxidative stress, chronic inflammation, and DNA methylation form a tightly interconnected regulatory axis rather than independent pathological events. This epigenetic – inflammatory interaction represents a central mechanism contributing to progressive muscle degeneration in sarcopenia.

Within skeletal muscle, DNA methylation can further modulate the transcriptional activity of genes involved in energy metabolism, ultimately impairing muscle performance [29]. For example, PGC-1α, a key regulator of cellular energy metabolism, is expressed at low levels or exhibits impaired function, leading to muscle atrophy and functional decline, thereby promoting sarcopenia [34]. Evidence suggests that DNA methylation can decrease PGC-1α transcriptional activity by inhibiting its promoter, thereby exacerbating mitochondrial dysfunction and muscle loss [35]. Moreover, altered methylation may dysregulate apoptosis-related genes, such as tumor protein P53 (*TP53*), leading to impaired cell-cycle control and apoptosis regulation, ultimately resulting in muscle dysfunction [36]. These results suggest that hypermethylation in skeletal muscle hampers the activity of genes essential for muscle development, disrupts myogenic differentiation and cellular function, and alters the regulation of apoptosis- and autophagy-associated genes. Collectively, these molecular disturbances accelerate the loss of muscle tissue and diminish contractile strength. The proposed mechanism of DNA methylation dysregulation in the pathogenesis of sarcopenia is illustrated in Figure 1.

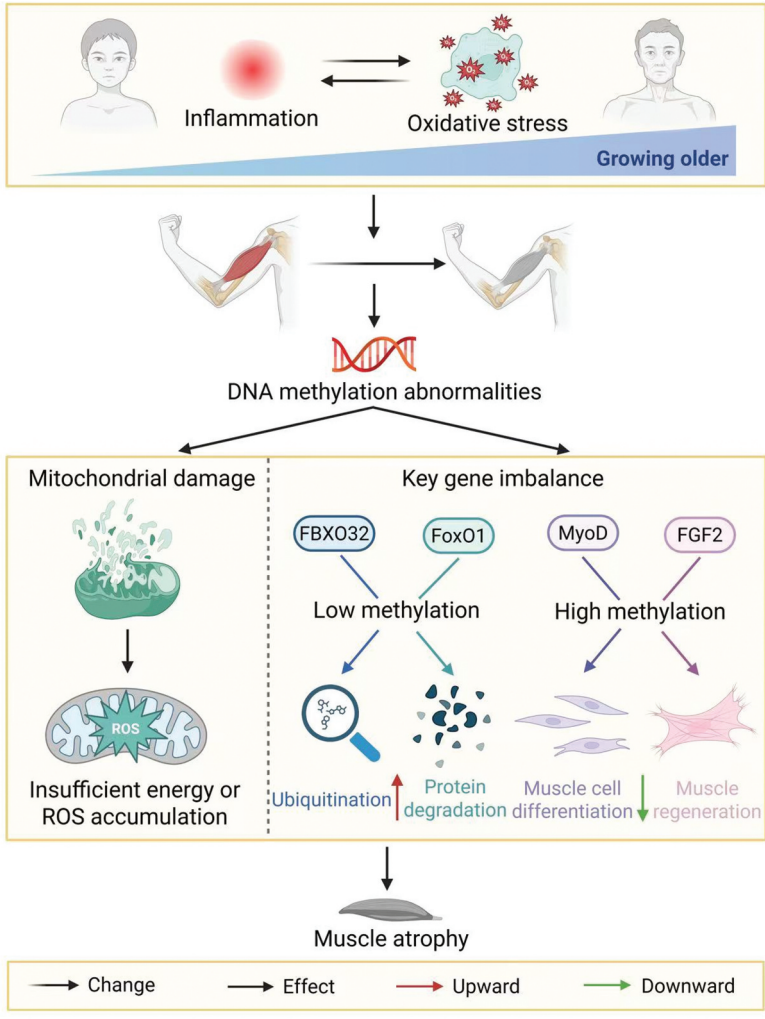

Figure 1. Epigenetic mechanisms of DNA methylation dysregulation in sarcopenia pathogenesis. Figure 1 is a conceptual diagram (created using BioRender.com) summarizing the reported mechanisms by which epigenetic dysregulation may contribute to sarcopenia. Chronic inflammation and oxidative stress are associated with aberrant DNA methylation in skeletal muscle. These changes include hypomethylation of atrophy-related genes (FBXO32/Atrogin-1, FoxO1, and FGF2), which is linked to enhanced ubiquitin – proteasome-mediated protein degradation and satellite cell depletion, as well as hypermethylation of regenerative genes (e.g., MyoD), which may suppress myogenic differentiation. These epigenetic alterations are also associated with mitochondrial dysfunction and energy insufficiency, contributing to increased ROS accumulation. Together, these processes impair skeletal muscle cell differentiation, regeneration, and proteostasis, ultimately contributing to progressive muscle atrophy.

Created in BioRender. Ding, F. (2025) https://BioRender.com/z56c7ax.

3.2. DNA methylation of key sarcopenia-related genes

Alterations in DNA methylation, whether hypermethylation or hypomethylation within promoter regions, can significantly influence skeletal muscle performance and its regenerative potential [37]. For example, epigenetic modifications of genes such as fibroblast growth factor 2 (*FGF2*), Forkhead box O1 (*FoxO*1), and *MyoD1* have been strongly associated with the onset and progression of sarcopenia [38]. Moreover, a range of additional genes exhibit characteristic DNA methylation alterations, further highlighting the pivotal role of epigenetic regulation in this condition [39].

3.2.1. Fibroblast growth factor 2

FGF2 is a key member of the fibroblast growth factor family and is located on the long arm of human chromosome 4 (4q). It encodes a multifunctional protein consisting of 288 amino acids. *FGF2* plays a pivotal role in skeletal muscle homeostasis and pathology, participating in multiple biological processes, including angiogenesis, cell proliferation, tissue repair, and developmental regulation [22].

In the early stages of sarcopenia, *FGF2* regulates muscle regenerative capacity by acting on skeletal muscle satellite cells. Under physiological conditions, *FGF2* promotes satellite cell activation and proliferation, thereby sustaining muscle fiber renewal and preserving muscle mass. However, with aging, aberrant DNA hypermethylation occurs in the *FGF2* gene promoter and in genes involved in its signaling pathway in skeletal muscle, leading to reduced *FGF2* transcription. This epigenetic suppression attenuates FGF2-induced proliferation in satellite cells, thereby impairing muscle regenerative capacity. Consequently, this process accelerates declines in muscle mass, strength, and physical function, thereby promoting the progression of sarcopenia [23].

During sarcopenia progression, altered DNA methylation at *FGF2*-related loci further contributes to disease pathogenesis. Evidence suggests that methylation levels at loci encoding secretory factors involved in skeletal muscle function significantly influence the onset and progression of sarcopenia [40]. Studies analyzing peripheral blood samples from individuals with sarcopenia revealed reduced DNA methylation at the FGF2-30 locus compared with non-sarcopenic controls, with further decreases correlating with disease severity [41].

From a phenotypic perspective, methylation levels at the FGF2-30 locus were positively correlated with multiple core sarcopenia indicators, including appendicular skeletal muscle mass index (ASMI), grip strength, and gait speed. Receiver operating characteristic (*ROC*) curve analysis indicated that a methylation level of 0.15 at this site demonstrated good diagnostic performance for sarcopenia, suggesting that *FGF2-30* methylation may serve as a potential epigenetic biomarker for early screening and severity assessment [42].

Notably, *FGF2* does not exert a uniformly protective effect in advanced sarcopenia or under dysregulated conditions. Fujii et al. suggested that age-related overexpression of *FGF2* may accelerate satellite cell depletion, thereby promoting skeletal muscle degeneration and atrophy [43]. These findings indicate that *FGF2* plays a stage-dependent role in sarcopenia development and progression, with moderate expression levels being crucial for maintaining skeletal muscle homeostasis.

3.2.2. Forkhead box O1

FoxO1 is a central member of the *FoxO* subfamily and plays a crucial role in energy metabolism, protein homeostasis, and cell fate regulation [44]. In pathological conditions characterized by disrupted skeletal muscle homeostasis, aberrant FoxO1 activation is recognized as a key molecular driver of muscle atrophy. In sarcopenia, *FoxO1* primarily remodels the muscle protein metabolic network through its actions in myofibers and satellite cells. Sustained *FoxO1* activation significantly enhances the transcription of genes associated with the ubiquitin – proteasome system (*UPS*) and the autophagy – lysosomal pathway, thereby accelerating muscle protein degradation and contributing to progressive declines in muscle mass and function [45].

However, transcriptional regulation alone cannot fully explain how *FoxO1* maintains persistently elevated activity in aging muscle. Kim et al. provided important mechanistic insight into this issue [46]. They demonstrated that protein arginine methyltransferase 5 *(PRMT5)* finely regulates *FoxO1* subcellular localization by controlling *FoxO1* protein arginine methylation, thereby influencing satellite cell fate determination and regenerative potential. When *PRMT5* expression or activity declines, FoxO1 protein arginine methylation is reduced. This reduction promotes abnormal cytoplasmic translocation of *FoxO1*, triggering excessive autophagy activation, particularly increased lipid droplet autophagy. This process depletes lipid droplet reserves in satellite cells, weakens their self-renewal capacity, and promotes premature differentiation, ultimately leading to depletion of the satellite cell pool and impaired muscle regenerative function. These findings directly link the epigenetic modification status of *FoxO1* to metabolism-dependent self-renewal mechanisms of satellite cells, providing a novel framework for understanding regenerative impairment in sarcopenia.

Additionally, studies on DNA methylation in the *FoxO1* promoter region have further elucidated the epigenetic basis of its age-related dysregulation. Evidence indicates that the *FoxO1* promoter region exhibits high methylation levels in young skeletal muscle. In contrast, methylation in this region significantly decreases in mature and aged muscle and shows a significant negative correlation with elevated *FoxO1* mRNA expression [47]. Functional analyses indicate that inhibition of *FoxO1* expression significantly promotes myoblast proliferation and differentiation, as evidenced by the coordinated upregulation of cell cycle – related genes (*PCNA*, *CDK2*, *CCND1*) and myogenic marker genes (*MyoD*, *MYOG*, *MYHC*). These findings suggest that DNA methylation events in the *FoxO1* promoter region may represent a key epigenetic driver of sarcopenia development.

3.2.3. Myogenic determinants

Myogenic determination factors, particularly *MyoD*, play a pivotal role in skeletal muscle lineage specification, differentiation, and regeneration by binding to E-box cis-regulatory elements within the promoters of target genes and activating downstream myogenic transcriptional programs [48,49]. Accumulating evidence indicates that *MyoD* dysfunction in

sarcopenia is neither an isolated nor a static event but is closely associated with epigenetic alterations. These alterations affect distinct myogenic cell populations at different stages of sarcopenia, ultimately leading to a progressive decline in skeletal muscle regenerative capacity.

During the early stages of sarcopenia, MyoD-related epigenetic alterations predominantly act as driving events affecting satellite cells and early myogenic progenitors. Genome-wide DNA methylation analyses have revealed a global hypermethylation pattern in aged human skeletal muscle, with particularly pronounced methylation changes at the *MyoD* locus [50]. Such aberrant methylation is associated with impaired differentiation potential of aged myogenic cells, as evidenced by significantly reduced expression of *MyoD* and its key downstream regulator, myogenin, during the late stages of induced differentiation (e.g., days 7 and 10) [51]. Because these epigenetic changes occur before overt muscle fiber loss, they are more likely to represent initiating mechanisms in sarcopenia development. Functionally, compromised activation of *MyoD*-dependent transcriptional programs directly impairs the transition of satellite cells from an activated state to differentiated myoblasts, thereby diminishing the regenerative reserve of skeletal muscle at early disease stages.

As sarcopenia progresses, chronic pathological conditions further reshape the epigenetic landscape of myogenic cells, giving rise to regulatory patterns characterized by secondary epigenetic alterations. Studies have shown that *MyoD* binding sites across the genome significantly overlap with differentially methylated regions (*DMRs*) in myoblasts, highlighting a critical role for DNA methylation in modulating *MyoD* transcriptional activity [52]. Investigations focusing on *TWIST1* provide further mechanistic insight: despite the presence of pro-myogenic transcriptional cues, hypermethylation in regions adjacent to the *TWIST1* promoter markedly suppresses its expression. The *TWIST1* protein, in turn, inhibits *MyoD* activity, thereby delaying myoblast differentiation into myotubes [53]. These secondary epigenetic alterations do not merely reduce *MyoD* expression levels but instead destabilize the *MyoD*-centered regulatory network, leading to delayed differentiation, reduced fusion efficiency, and incomplete muscle repair. Collectively, these alterations exacerbate the muscle degeneration phenotype observed in advanced disease stages.

Beyond disease-specific mechanisms, aging itself introduces systemic instability into the *MyoD* regulatory network through epigenetic drift. Epigenetic drift is typically characterized by the progressive accumulation of age-associated alterations in DNA methylation patterns, which broadly undermine the precision of transcriptional regulation rather than affecting individual genes in isolation. Studies on *MyoD*-mediated cellular reprogramming provide essential insights into this process. *MyoD* can directly reprogram fibroblasts into mature myocytes or convert them into induced myogenic progenitor cells (*iMPCs*) [54]. The stable generation of *iMPCs* relies on *TET* enzyme – mediated active DNA demethylation, which markedly enhances chromatin accessibility at loci associated with muscle stem cell identity, such as *Pax7* and *Myf5* [55]. In contrast, reprogramming strategies based solely on *MyoD* overexpression induce relatively limited methylation remodeling, resulting in myotubes that fail to maintain endogenous *MyoD* expression and exhibit unstable myogenic identity, with a high propensity for phenotypic reversion [55]. Collectively, these findings suggest that epigenetic abnormalities associated with *MyoD* in sarcopenia constitute a multilayered and dynamically evolving process.

3.2.4. Other genes

Beyond classical regulatory factors, the onset and progression of sarcopenia also involve aberrant DNA methylation across multiple genes, reflecting hierarchical epigenetic contributions to disease initiation and progression, as well as age-related epigenetic drift. In the early stages of sarcopenia, epigenetic alterations that directly compromise myofibrillar stability and protein homeostasis appear to function as primary disease drivers. Among these, myomesin-2 (*MYOM2*) may represent a critical early regulatory factor. *MYOM2* encodes a core M-band protein essential for maintaining sarcomere alignment and structural stability during muscle contraction [56]. Reduced methylation at the *MYOM2* locus has been observed in sarcopenia-prone populations, accompanied by increased gene expression. Dysregulated *MYOM2* expression disrupts the balance of sarcomeric components, leading to myofibrillar structural damage, impaired force transmission, and early functional decline in muscle [57]. In addition, myosin filament instability may alter the mechanical microenvironment of skeletal muscle, indirectly suppressing satellite cell activation and impairing regenerative capacity. Collectively, these findings suggest that *MYOM2* hypomethylation represents an early epigenetic driver centered on structural impairment rather than merely an age-associated change.

Concurrently, integrative machine learning – based analyses have demonstrated significant associations between hypomethylation of specific genes and sarcopenia susceptibility. Reduced methylation of *FBXO32* (encoding Atrogin-1) and *TRIM63* (encoding *MuRF1*) enhances transcriptional activation of ubiquitin – proteasome system – related genes, thereby accelerating myofibrillar protein degradation. Such alterations shift protein homeostasis toward net loss, exacerbating muscle atrophy. In contrast, hypomethylation of histone deacetylase genes (e.g., *HDAC4* and *HDAC5*) may impede muscle repair and differentiation by reinforcing repressive chromatin states. Furthermore, methylation alterations in myofiber type – specific genes (e.g., *MYH1*, *MYH2*, *MYH6*, *MYH7*, and *MYL3*) disrupt the dynamic equilibrium between fast- and slow-twitch fibers, thereby impairing contractile function [58]. These alterations are more consistent with epigenetic responses characteristic of disease amplification, representing a maladaptive remodeling process that ultimately culminates in dysfunction under chronic degenerative conditions.

In summary, current evidence indicates that DNA methylation changes in sarcopenia constitute a multi-tiered epigenetic framework with distinct functional roles. These include driver epigenetic events initiating muscle atrophy, secondary modifications that accelerate disease progression, and age-related epigenetic drift that amplifies individual susceptibility. Clarifying these layers not only deepens our understanding of sarcopenia pathogenesis but also facilitates the linkage of specific methylation signatures to disease stages and cellular targets, thereby enhancing the translational potential of epigenetic biomarkers. The key DNA methylation alterations and their phenotypic associations discussed above are systematically summarized in Table 1.

Table 1. Association between the methylation status of key genes and muscle phenotype.

Disease model/ cell model	Representative gene(s)	Methylation site(s)	Trend of DNA methylation levels	Mechanisms	References
Aging muscle	PGC-1α	Promoter region	Hypermethylation↑	PGC-1α hypermethylation ➡ Transcriptional suppression ➡ Mitochondrial dysfunction ➡ Muscle atrophy	[34,35]
Spinal cord injury mice	*FBXO32 (Atrogin-1)*	Promoter region	Hypomethylation↓	*FBXO32* hypomethylation ➡ Ubiquitin-proteasome activity↑ ➡ Muscle protein degradation↑	[39,58]
Human skeletal muscle tissue	*MYH2*	Promoter region	Hypomethylation↓	*MYH2* hypomethylation ➡ Fast-twitch fiber proportion↓➡ Contractile dysfunction	[39,58]
Sarcopenia patients (whole blood)	FGF2	FGF2-*30* locus	Hypomethylation↓	Low methylation at *FGF2*-30 ➡ *FGF2* expression↑➡ Correlates with reduced ASMI, grip strength, gait speed	[41,42]
Aging human skeletal muscle	*FGF2*	Promoter (e.g., *FGF2-30* locus)	Hypomethylation↓	*FGF2* hypomethylation ➡ *FGF2* expression↑ ➡ Satellite cell depletion ➡ Muscle regeneration↓ ➡ Sarcopenia	[41–43]
PRMT5-deficient models	*FoxO1*	Arginine residues (by PRMT5)	Hypomethylation↓	*FoxO1* hypomethylation ➡ Cytoplasmic translocation ➡ Lipophagy↑➡ Satellite cell depletion ➡ Impaired regeneration	[46]
Aged muscle tissue	*FoxO1*	Promoter region	Hypomethylation↓	*FoxO1* hypomethylation ➡ *FoxO1* expression↑➡ UPP/autophagy activation ➡ Protein degradation ↑➡ Muscle atrophy	[47]
Aged human myoblasts	*MyoD*	Promoter-proximal regions	Hypermethylation↑	*MyoD* hypermethylation ➡ *MyoD/Myogenin* expression↓ ➡ Satellite cell activation↓➡ Myogenic differentiation↓	[50,51]
Transdifferentiation models	*MyoD* target genes	DMRs (e.g., TWIST1 promoter)	Hypermethylation↑	TWIST1 hypermethylation ➡ TWIST1 suppression↓➡ *MyoD* inhibition ➡ Delayed myotube formation	[52,53]
Muscle atrophy patients	*MYOM2*	Promoter region	Hypomethylation↓	*MYOM2* hypomethylation ➡ Sarcomere destabilization ➡ Myofibril dysfunction ➡ Impaired satellite cell function	[56,57]

Note: The symbols "↑" (red) and "↓" (green) indicate increased (hypermethylation) or decreased (hypomethylation) DNA methylation levels at key regulatory sites. Table 1 presents a conceptual summary based on published studies, illustrating how epigenetic alterations in sarcopenia-related genes are associated with muscle atrophy through specific molecular pathways.

4. Roles of chromatin remodeling in sarcopenia

Chromatin remodeling refers to an ATP-dependent process in which chromatin regulatory complexes modulate gene transcription by altering nucleosome positioning and chromatin accessibility [59]. Compared with DNA methylation, chromatin remodeling is more dynamic, enabling rapid responses to metabolic stress, mechanical loading changes, and inflammatory microenvironments. In sarcopenia, abnormal chromatin remodeling is not a single event but occurs across multiple stages of disease onset and progression, exerting distinct effects in different cell types [60]. Elucidating the role of chromatin remodeling in sarcopenia is crucial for understanding its pathophysiology and enabling stage-specific interventions.

4.1. Modulating muscle gene expression

Chromatin remodeling plays a central regulatory role in the onset and progression of sarcopenia by dynamically modulating chromatin structure and transcriptional accessibility. Compared with individual gene expression changes, this mechanism systematically reshapes the response patterns of muscle cells to aging-related stimuli. Emerging evidence indicates that chromatin remodeling is not merely a passive byproduct of sarcopenia but an active driver shaping disease trajectories across stages and cell types [61].

In the early stages of sarcopenia, abnormal chromatin remodeling primarily affects skeletal muscle satellite cells, leading to a latent impairment of their compensatory regenerative capacity. Under normal conditions, ATP-dependent chromatin remodeling complexes (e.g., SWI/SNF) maintain an open chromatin state at myogenic gene promoters and enhancers, enabling satellite cells to respond effectively to injury or metabolic stimuli [62]. Recent studies, including those on *BAF60c*, demonstrate at the chromatin level that sarcopenia-related alterations stem not only from reduced satellite cell numbers but also from diminished transcriptional plasticity [63]. Using muscle-specific genetic manipulation models, researchers found that *BAF60c* synergizes with *MEF2C* to regulate chromatin accessibility at specific myogenic and secretory factor gene loci [64,65]. This finding advances understanding of satellite cell functional decline, moving beyond the traditional cell-depletion paradigm to an epigenetically regulated disorder, providing a new conceptual framework for early intervention.

As sarcopenia progresses, abnormal chromatin remodeling gradually extends to mature muscle fibers, directly contributing to the transcriptional suppression of protein metabolism and regenerative programs. HDACs are persistently activated at this stage, systemically inhibiting the transcriptional activity of myogenic transcription factors by reducing chromatin accessibility [66]. Compared with earlier studies that primarily viewed HDACs as transcriptional repressors during myogenesis, recent research has expanded their functional scope. It suggests that HDACs may also indirectly modulate the mechanical characteristics and redox microenvironment of satellite cells by reprogramming the transcriptional landscape of extracellular matrix-associated genes [67,68]. This mechanism provides a plausible explanation for the phenomenon of preserved satellite cell numbers yet limited regenerative capacity in aged muscle, highlighting chromatin remodeling's pivotal role as a hub linking intracellular transcriptional regulation and microenvironmental changes.

In advanced sarcopenia, dysregulated chromatin remodeling exhibits synergistic amplification across cell types, including myofibers, satellite cells, and interstitial muscle cells. At this stage, sustained downregulation of *BAF60c* not only weakens myogenic transcriptional networks but also blocks myogenic stem cell differentiation by inhibiting Six4-dependent

pathways and upregulating the inhibitory secretory factor *Dkk3* [69,70]. Such studies extend the scope of chromatin remodeling from intracellular transcriptional regulation to the systematic reorganization of intercellular signaling networks, revealing how epigenetic abnormalities in sarcopenia form degenerative amplification loops through secretory factor – mediated signaling pathways. However, it should be noted that existing evidence primarily originates from animal models or in vitro systems. Whether these mechanisms exhibit identical temporal sequences and intensities in human populations requires validation through longitudinal studies.

Collectively, studies of chromatin remodeling have established an epigenetic regulatory framework that explains the progressive, largely irreversible pathological features of sarcopenia. Together, these findings indicate that declining chromatin plasticity constitutes a pivotal hub in the transition from functional compensation to structural deterioration in muscle. Although current research faces limitations in extrapolating models and validating causal mechanisms, this field has laid a solid theoretical foundation for developing precision intervention strategies targeting chromatin regulatory factors. It also highlights future directions for in-depth exploration, including the integration of single-cell and spatial epigenomics technologies.

4.2. Governing fiber-type transition

The composition of skeletal muscle fiber types directly determines contractile properties and force output, and its dynamic equilibrium depends on coordinated transcriptional regulation and chromatin remodeling mechanisms [71]. Aging and sarcopenia are characterized by a selective reduction in fast-twitch (type II) fibers and a relative increase in slow-twitch (type I) fibers, representing a hallmark structural alteration. This shift is primarily driven by chromatin remodeling – mediated reprogramming of gene expression profiles [72].

During the early, initial stages of sarcopenia, chromatin remodeling primarily acts on differentiated, mature myofibers. By modulating chromatin accessibility at loci specific to fast- and slow-twitch genes, it regulates myofiber phenotypic plasticity. Under physiological conditions, fast- and slow-twitch – associated genes maintain a reversible equilibrium via specific enhancer – promoter interactions, enabling adaptive responses to neural input and metabolic demand [73]. However, aging-associated declines in chromatin remodeling capacity gradually disrupt this regulatory equilibrium [74]. Studies indicate that transcription factors such as kruppel-like factor 5 (*KLF5*) and activator protein 1 (*AP-1*) recruit chromatin remodeling complexes to modulate the chromatin architecture of myofibrillar type – determining genes, including *MYH4* and *MYH7*. Under sarcopenia-associated stress, these regulatory axes preferentially maintain open chromatin states at slow-twitch fiber genes while suppressing activation of fast-twitch programs. This transcriptional bias may initially represent a compensatory adaptation to reduced energetic efficiency. However, progressive stabilization of chromatin states ultimately impairs fast-twitch fiber recovery and sustains declines in force output [55]. At this stage, chromatin remodeling alterations are not primary drivers but rather secondary epigenetic changes that emerge during disease progression.

In mid-to-late stages, aberrant chromatin remodeling further stabilizes and amplifies myofibrillar type conversion, resulting in long-term maintenance of a low-power, oxidative phenotype. The *STARD7*-associated super-enhancer network plays a pivotal role in this process. By enhancing transcription of slow-twitch and oxidative metabolism – related genes, it promotes the transition from glycolytic to oxidative fibers. This mechanism primarily affects the metabolic and contractile functions of mature myofibers. It is accompanied by mitochondrial dysfunction and *ROS* accumulation, ultimately reducing fatigue resistance and explosive power [75].

Furthermore, ELK family member 4 (*ELK4*), a transcriptional regulator, influences myofiber type conversion by modifying chromatin states at fast- and slow-twitch gene loci and by interacting with the transforming growth factor beta 1 (TGF-β1) signaling pathway [58]. ELK4-mediated chromatin remodeling not only disrupts the balance between fast/slow gene expression but also activates fibrosis-associated transcriptional programs, thereby enhancing extracellular matrix deposition. This process involves interactions between mature myofibers and interstitial cells, indirectly suppressing fast-twitch fiber maintenance and regenerative capacity by altering the mechanical properties of the muscle microenvironment [56]. This mechanism represents secondary epigenetic reprogramming during disease progression. Once established, however, it markedly limits the reversibility of myofibrillar phenotypes.

Notably, some age-related myofibrillar chromatin alterations reflect epigenetic drift, characterized by a gradual convergence in chromatin accessibility across fiber types. Although insufficient alone to dictate fiber-type conversion, this drift reduces myofiber responsiveness to neural stimulation, exercise, and metabolic cues, thereby creating a permissive background for disease-associated chromatin remodeling abnormalities [57]. Against this background, secondary epigenetic alterations become more readily stabilized as long-term pathological states, accelerating sarcopenia-associated functional decline.

4.3. Regulating mitochondrial function

Mitochondrial dysfunction is considered a core pathological mechanism in the onset and progression of sarcopenia, characterized by reduced respiratory chain complex activity, decreased ATP production, and excessive *ROS* accumulation, ultimately leading to energy insufficiency and functional decline in myofibers [76,77]. However, accumulating evidence indicates that mitochondrial damage is not solely driven by aging or metabolic imbalance but is dynamically regulated by multi-level epigenetic mechanisms across different disease stages [78,79]. Therefore, clarifying the temporal sequence and causal roles of these regulatory processes is crucial for distinguishing driver alterations from secondary responses arising during disease progression.

In early or subclinical stages of sarcopenia, certain chromatin remodeling – related alterations may precede overt myofibrillar atrophy, suggesting a potential driver role in epigenetic regulation. Among these, BAF60c, a subunit of the SWI/SNF chromatin

remodeling complex, serves as a key node linking chromatin structural regulation to mitochondrial metabolic programs. Studies indicate that BAF60c interacts with the transcription factor Six4 to induce *DEPTOR* expression. This interaction promotes glycolytic metabolism and mitochondrial biogenesis via the AKT signaling pathway, thereby sustaining skeletal muscle metabolic activity [65]. Under sarcopenia-associated pathological conditions, BAF60c expression is suppressed, leading to mitochondrial dysfunction and metabolic imbalance. This alteration not only compromises energy metabolism in mature myofibers but also diminishes satellite cell adaptability to high energy demands and regenerative capacity [69]. Consequently, BAF60c-mediated chromatin remodeling abnormalities likely represent an early regulatory event in mitochondrial dysfunction rather than a secondary consequence of disease progression.

In contrast, the arginine methyltransferase CARM1 modulates gene transcription by inducing chromatin conformational changes through modification of NuRD complex – associated subunits [80]. Under physiological conditions, CARM1 maintains mitochondrial integrity and oxidative metabolism by regulating *PPARGC1A* and its downstream mitochondrial-associated genes (e.g., *TFAM*, *NFE2L2*). However, CARM1 dysfunction disrupts chromatin remodeling, inhibits mitophagy, and impairs mitochondrial turnover, ultimately leading to energy metabolism disorders and myofiber atrophy [81]. Such regulatory abnormalities not only affect mature myofibers but may also indirectly reduce the proliferation and differentiation capacity of muscle satellite cells by compromising mitochondrial homeostasis. Because these epigenetic alterations can precede overt muscle atrophy, existing evidence supports CARM1 as a potential driver in sarcopenia.

As the disease progresses, mitochondrial dysfunction worsens, characterized by declining NAD^+ levels, increased oxidative stress, and chronic low-grade inflammation. Under these conditions, specific epigenetic regulatory mechanisms tend to manifest as secondary responses to the pathological microenvironment. Sirtuins (SIRTs), as NAD^+-dependent deacetylases, participate in chromatin remodeling by regulating histone acetylation and promote mitochondrial biogenesis and oxidative metabolism through deacetylation of PGC-1α [82,83]. In multiple experimental models, sirtuins partially delay muscle functional decline by increasing mitochondrial DNA content, improving respiratory function, and regulating mitochondrial fusion – associated proteins (e.g., *MFN1*). However, during sarcopenia progression, sustained NAD^+ depletion limits sirtuin activity, leading to a progressive failure of compensatory and protective epigenetic regulation, thereby further amplifying mitochondrial dysfunction [84]. Therefore, sirtuin-related alterations more accurately reflect secondary, metabolically stress – driven epigenetic dysregulation during disease progression rather than serving as initial triggers of sarcopenia onset.

Collectively, existing evidence indicates that mitochondrial dysfunction constitutes a key pathological basis of sarcopenia development and is dynamically regulated by multi-level epigenetic mechanisms. This perspective challenges the traditional view that primarily attributes mitochondrial dysfunction to aging or metabolic decline and provides a theoretical foundation for early risk identification and molecular subtyping of sarcopenia. However, current conclusions are mainly derived from animal models and in vitro studies. Their applicability to clinical populations, temporal causality, and translational relevance requires further validation.

5. Roles of ncRNAs in sarcopenia

In recent years, the role of ncRNAs in sarcopenia has attracted increasing attention. These molecules, including miRNAs, lncRNAs, and circRNAs, have been implicated in both the pathogenesis and progression of sarcopenia [85]. Unlike DNA methylation and chromatin remodeling, ncRNAs primarily exert regulatory effects at the post-transcriptional level. They influence disease onset and progression by modulating established gene expression programs and disease-related signaling networks [86].

5.1. MicroRNAs

MiRNAs are small endogenous non-coding RNAs, typically 20–25 nucleotides in length, that play crucial roles in pathways related to muscle protein synthesis, degradation, and metabolism. Dysregulation of specific miRNAs that act on satellite cells represents an early driver of impaired muscle regeneration and repair capacity. miRNAs directly influence satellite cell fate by regulating key transcription factors and signaling pathways [87]. For example, miR-206 targets and suppresses the transcription factors *Pax3* and *Pax7*, thereby promoting satellite cell differentiation toward the myogenic lineage and enhancing muscle repair [88]. However, during aging and certain pathological conditions, downregulation of miR-206 weakens its repression of *Pax3* and *Pax7*, impairing satellite cell differentiation and reducing repair capacity following muscle injury. Similarly, age-related reduction of miR-143 expression relieves its inhibitory effect on insulin-like growth factor-binding protein 5 (*IGFBP5*). Elevated *IGFBP5* may promote satellite cell senescence, leading to depletion of their proliferative and differentiative potential [89]. Furthermore, one study reported significantly elevated serum miR-451a levels in patients with sarcopenia compared with healthy controls, with a further increase observed after rehabilitation, suggesting its involvement in disease pathogenesis. Bioinformatic analyses indicate that miR-451a directly targets the 3′ untranslated region (3′UTR) of the titin (*TTN*) gene, a key structural protein in muscle fibers, thereby suppressing *TTN* expression at the post-transcriptional level. This may represent a critical mechanism affecting muscle structure and function. The sustained elevation of miR-451a after recovery may indicate activation of a compensatory repair pathway following muscle injury [90]. Collectively, these alterations contribute to depletion of the myogenic precursor pool and blunted regenerative responses at the cellular level, constituting an important mechanism underlying the failure to maintain muscle mass in sarcopenia.

Conversely, miRNAs can concurrently target protein synthesis and degradation pathways, disrupting protein

homeostasis in myofibers and promoting muscle atrophy [91]. For instance, miR-7a-1-3p exacerbates metabolic imbalance through a dual mechanism: it suppresses androgen receptor (*AR*) expression, thereby hindering myosin synthesis, and inhibits *IGF-1*–mediated activation of the Akt/mTOR signaling pathway, further impairing protein synthesis and potentially promoting degradation pathways [92]. In contrast, certain miRNAs exert protective effects under physiological conditions. MiR-486 activates the PI3K/AKT signaling pathway and suppresses the transcription factor *FoxO1*, thereby downregulating the atrophy-related genes *Atrogin-1* and *MuRF1* and inhibiting protein degradation mediated by the ubiquitin – proteasome pathway [93]. The regulatory network formed by these miRNAs within muscle fibers directly determines net protein balance, and its disruption constitutes a critical step in muscle fiber atrophy.

Additionally, miRNAs regulate muscle metabolism and inflammatory responses. Dysregulation of specific miRNAs can lead to mitochondrial dysfunction, which is closely associated with muscle weakness and increased fatigue susceptibility. Evidence indicates that miR-129-3p increases intracellular nicotinamide adenine dinucleotide (NAD^+) levels by inhibiting poly (ADP-ribose) polymerase 1 (*PARP1*), thereby activating the deacetylase sirtuin 1 (*SIRT1*). Activated *SIRT1* promotes deacetylation of PGC-1α, enhancing mitochondrial biogenesis and function, which ultimately improves muscle strength and metabolic adaptability [94]. This finding reveals a key molecular pathway underlying miRNA-mediated regulation of mitochondrial function. It provides theoretical support and potential therapeutic targets for precision interventions focused on miRNA-guided modulation of energy metabolism. In contrast, certain miRNAs modulate the local microenvironment by regulating inflammatory responses. For example, miR-1245a, which is significantly elevated in patients with sarcopenia, interferes with the JAK – STAT signaling pathway and cytoskeletal organization, inhibits immune cell activation, and is closely associated with inflammatory processes [95]. Therefore, a deeper understanding of the mechanisms and pathways through which different miRNAs function in muscle tissue is essential for the prevention and treatment of sarcopenia.

5.2. Long noncoding RNAs

LncRNAs are transcripts longer than 200 nucleotides that generally lack protein-coding capacity [96]. Unlike miRNAs, lncRNAs exhibit diverse mechanisms of action. They regulate gene transcription through cis- or trans-acting mechanisms, serve as molecular scaffolds or signaling mediators, and function as miRNA sponges. lncRNAs participate in the modulation of chromatin states, transcription factor activity, and the integration of signaling pathways [97,98].

In mature muscle fibers, certain lncRNAs influence skeletal muscle energy metabolism by regulating mitochondrial homeostasis, representing a key molecular basis of sarcopenia development. Yu et al. reported that lncRNA *Gm20743* functions within the mitochondrial regulatory network of myofibers, alleviating oxidative stress while enhancing oxidative phosphorylation and glutathione metabolism. This preserves mitochondrial structural and functional integrity, thereby supporting cellular energy supply and metabolic homeostasis in myocytes [99]. These findings indicate a protective regulatory role for *Gm20743* in skeletal muscle; reduced expression may impair myocyte adaptation to metabolic stress and, in turn, promote myofibrillar functional decline. Conversely, certain lncRNAs exert pro-pathogenic effects by disrupting mitochondrial homeostasis. Aparicio et al. demonstrated that lncRNA *PVT1* induces mitochondrial dysfunction and reduces cellular energy efficiency by downregulating c-Myc and upregulating the anti-apoptotic protein Bcl-2 [100]. This metabolic abnormality is not incidental; it impairs skeletal muscle cell adaptability, activates proteolytic pathways, and accelerates myofibrillar atrophy. This suggests *PVT1* may serve as an upstream driver in sarcopenia progression, with metabolic imbalance at its core. Additionally, lncRNAs influence the ubiquitin – proteasome and autophagy pathways involved in myofibrillar protein degradation. Among these, lncRNA *SYISL* primarily acts in mature muscle fibers. By competitively binding miR-103-3p, miR-205-5p, and miR-23a-3p, *SYISL* upregulates key atrophy-related factors such as MuRF1, FoxO3a, and Atrogin-1, thereby enhancing post-transcriptional protein degradation signaling [101]. Furthermore, *SYISL* interacts with Polycomb repressive complex 2 (PRC2), inhibiting the transcriptional activity of p21 and myogenin, thereby blocking satellite cell differentiation at the chromatin epigenetic level. This dual regulatory mechanism, which simultaneously modulates protein metabolism in mature myofibers and muscle regeneration, positions *SYISL* as a pivotal molecular hub linking enhanced proteolysis with impaired regenerative capacity. Furthermore, lncRNAs significantly influence cell proliferation, differentiation, and maintenance of cell fate. Zheng et al. demonstrated that upregulation of lncRNA *PRKG1-AS1* suppresses the expression of key myogenic transcription factors, including *MyoD*, myogenin, MEF2C, and *Myf5*, markedly reducing myoblast differentiation potential and inducing apoptotic signaling, thereby limiting muscle regenerative capacity [102]. This further demonstrates that lncRNAs can systematically suppress myogenic transcriptional networks, accelerating the depletion of muscle regenerative function. Concurrently, the downregulation of certain lncRNAs warrants equal attention. lncRNA *GPRC5D-AS1* is markedly reduced in sarcopenic skeletal muscle. Its normal function involves directly binding to and stabilizing SLC7A11 mRNA and protein, thereby promoting glutathione synthesis and inhibiting lipid peroxidation and ferroptosis [103]. However, insufficient *GPRC5D-AS1* expression increases susceptibility to oxidative stress and ferroptosis, thereby amplifying myocyte loss and muscle fiber atrophy. Furthermore, lncRNAs influence the long-term stability of the skeletal muscle microenvironment by regulating cellular senescence and fibrosis-related signaling pathways. Downregulation of lncRNA *MALAT1* releases inhibition of miR-34a-5p, suppresses *SIRT1* activity, and induces cellular senescence. Concurrently, reduced *MALAT1* expression activates the TGF-β1 signaling pathway, promoting myofibrillar fibrosis and further limiting regeneration and functional recovery [104]. This dual regulation of aging and fibrosis processes positions *MALAT1* as a crucial regulator for maintaining skeletal muscle structural and functional homeostasis.

At the protein level, lncRNAs influence ribosome biogenesis and mRNA stability, thereby directly determining the sustained synthetic capacity of myofibrillar structural proteins [105]. Sen et al. found that downregulation of lncRNA *TMEM9B-AS1* weakens the binding and stabilizing effects of IGF2BP1 on *MYC* mRNA, leading to accelerated *MYC* protein degradation and insufficient ribosome production, thereby inhibiting actin and myosin synthesis [106]. This regulatory mechanism directly links alterations in lncRNA expression to impaired maintenance of myofibrillar structure, constituting a key molecular basis for structural atrophy in sarcopenia.

Given the diverse and complex regulatory roles of lncRNAs, elucidating the causal functions of specific lncRNAs across different cell types and regulatory layers is essential for understanding the molecular basis of sarcopenia and developing precision intervention strategies.

5.3. Circular RNAs

CircRNAs are a class of non-coding RNAs characterized by covalently closed circular structures. Due to the absence of a 5′ cap and a 3′ poly(A) tail, circRNAs exhibit enhanced structural stability. Consequently, compared with miRNAs and lncRNAs, circRNAs accumulate more readily in aging tissues and exert more sustained regulatory effects [107,108].

In mature skeletal muscle fibers, certain circRNAs directly disrupt myofibrillar homeostasis by encoding atrophy-promoting peptides or by inducing inflammatory signaling cascades [109]. Studies have shown that circTmeff1 is significantly upregulated in multiple sarcopenia models and amplifies muscle atrophy signaling through dual mechanisms, in addition to transcriptional regulation. CircTmeff1 interacts with TAR DNA-binding protein 43 (TDP-43), promoting its aberrant aggregation within myocyte mitochondria. This interaction stimulates the release of mitochondrial DNA (mtDNA) into the cytoplasm, thereby activating the cyclic GMP-AMP synthase (cGAS) – stimulator of interferon genes (STING) innate immune pathway and triggering sustained inflammatory and proteolytic signaling. Concurrently, circTmeff1 produces the atrophy-promoting peptide TMEFF1-339aa via IRES-dependent circular translation, directly intensifying catabolic processes within myofibers [110]. This synergistic interaction between inflammatory amplification and translation-dependent mechanisms establishes a coherent causal framework for circTmeff1-mediated myofibrillar atrophy. Similarly, circDdb1 exhibits sustained upregulation in aging- or disuse-associated muscle atrophy models, with its primary effect centered on the imbalance between protein synthesis inhibition and degradation enhancement. circDdb1 produces circDdb1-867aa through rolling-circle translation. This peptide binds to elongation factor eEF2 and enhances phosphorylation at Thr56, thereby inhibiting global translation elongation. Concurrently, circDdb1-867aa synergistically activates the ubiquitin – proteasome system and autophagy – lysosomal pathways, accelerating myofibrillar protein degradation. At the upstream regulatory level, eukaryotic initiation factor 4A3 (EIF4A3) promotes circDdb1 circularization, forming a positive feedback loop that sustains protein synthesis inhibition and enhanced degradation, thereby stabilizing the muscle atrophy phenotype [111]. In pathological contexts characterized by inflammation and stress responses, certain circRNAs remodel inflammatory and apoptotic signaling pathways through the miRNA sponge mechanism, thereby indirectly disrupting muscle homeostasis. circAGO3 exemplifies this process by sponging miR-34b-5p to upregulate *TRAF3* expression, thereby persistently activating the NF-κB signaling pathway. In skeletal muscle cells, chronic NF-κB activation promotes the release of inflammatory cytokines, directly induces the expression of proteolysis-related genes, such as Atrogin-1 and MuRF1, and exacerbates oxidative stress and apoptosis. Consequently, circAGO3 forms an amplification loop linking inflammatory signaling, protein degradation, and cell death, thereby driving sarcopenia toward irreversible progression [112].

Additionally, at the neuromuscular axis level, certain circRNAs indirectly contribute to sarcopenia by regulating RNA metabolic networks and neuronal homeostasis. Studies have shown that in neurogenic muscle atrophy disorders such as spinal muscular atrophy (SMA), circRNA C2A-2B-3–4 is significantly downregulated, and its loss leads to reduced expression of genes involved in ribosome biogenesis, RNA metabolism, and protein synthesis (e.g., *NAMPT*, *CELSR3*), while also causing dysregulation of genes associated with axonal growth and synaptic maintenance, thereby impairing neuromuscular signaling efficiency [113]. Similarly, circ4-2b-3 interferes with the stability and splicing of full-length *SMN* mRNA by competitively binding miRNAs or RNA-binding proteins, thereby accelerating α-motor neuron degeneration and ultimately inducing secondary muscle atrophy [114]. These findings suggest that circRNAs exert effects not only within muscle cells but also influence muscle structure and function through neural regulatory pathways.

In contrast, certain circRNAs exert protective regulatory roles in sarcopenia, and their absence or downregulation may constitute pathogenic factors. circCCDC91 primarily functions in muscle satellite cells during proliferation and differentiation. By competitively binding miR-15 family members, circCCDC91 relieves their inhibition of IRS1, thereby maintaining activation of the IGF-1–PI3K/AKT signaling pathway. This pathway not only promotes myoblast proliferation and differentiation but also suppresses FoxO1-mediated expression of proteolytic genes. When circCCDC91 expression declines, AKT signaling is impaired, muscle regenerative capacity decreases, and proteolytic signaling becomes dominant, ultimately accelerating sarcopenia progression [115]. Thus, circCCDC91 expression status partially reflects the preservation of muscle synthetic and regenerative capacity and may hold potential value for disease monitoring.

Collectively, the diverse epigenetic mechanisms of circRNAs are involved throughout the pathophysiological process of sarcopenia. Specific circRNAs are implicated in early satellite cell dysfunction, mid-stage protein homeostasis imbalance, and late-stage irreversible muscle fiber loss. These characteristics position circRNAs not only as valuable entry points for mechanistic research but also as promising biomarkers and potential therapeutic targets for sarcopenia. Future research should further elucidate their temporal dynamics and cell-type

specificity while exploring translational strategies for clinical application. The essential features and mechanisms of noncoding RNAs in sarcopenia are systematically summarized in Table 2. An integrated regulatory network of noncoding RNAs in the pathogenesis of sarcopenia is depicted in Figure 2.

6. Conclusion

Epigenetic research offers key mechanistic insight into the onset and progression of sarcopenia. It explains how reversible regulators, DNA methylation, chromatin remodeling, and ncRNAs shape muscle differentiation, protein synthesis and

Table 2. Essential features of the roles of noncoding RNAs in the regulation of sarcopenia.

Models	Trend of non-coding RNA	Target molecules	Mechanisms	Outcome event	References
Aged muscle tissue	miR-206↓	*Pax3, Pax7*	miR-206↓➡ *Pax3*/*Pax7* inhibition↓➡ Satellite cell differentiation↓➡ Muscle repair↓	Impaired muscle regeneration	[88]
Aging muscle	miR-143↓	*IGFBP5*	miR-143↓➡*IGFBP5* inhibition↓➡ *IGFBP5*↑➡ Satellite cell senescence↑➡ Functional decline↑	Satellite cell senescence, muscle function decline	[89]
Sarcopenia patients (serum)	miR-451a↑	*TTN* (titin)	miR-451a ↑➡ *TTN* mRNA targeting (3′UTR) ➡ *TTN* expression↓➡ Muscle structure/function impairment	Potential compensatory repair after injury	[90]
Aged male rats	miR-7a-1-3p↑	AR, IGF-1	miR-7a-1-3p↑➡ AR↓ & IGF-1-Akt/mTOR inhibition ➡ Myogenic protein synthesis ↓ & Protein degradation↑	Imbalance in protein metabolism (synthesis ↓ & degradation↑)	[92]
Muscle atrophy mice and C2C12 cells	miRNA-486↓	*FOXO1*	miRNA-486↑➡ PI3K/AKT activation↑➡ FOXO1↓➡ *Atrogin-1/MuRF1*↓➡ Protein degradation↓ (Note:↑ miRNA-486 is protective)	Slowed protein degradation	[93]
Mouse-derived C2C12 myotube model	miR-129-3p↓	*PARP1*	miR-129-3p↑➡*PARP1*↓➡NAD+↑➡SIRT1 activation↑➡ PGC-1α deacetylation↑➡ Mitochondrial function↑➡ Muscle strength↑	Mitigation of muscle atrophy (Note: ↑ miR-129-3p is protective)	[94]
Sarcopenia patients	miRNA-1245a↑	JAK-STAT pathway, actin cytoskeleton	miRNA-1245a↑➡ JAK-STAT pathway modulation ➡ Satellite cell activity↓ ➡ Muscle regeneration↓	Onset and progression of sarcopenia	[95]
Muscle atrophy mice and C2C12 cells	Gm20743↓	ROS, oxidative phosphorylation	Gm20743↑➡ ROS generation↓ & Oxidative phosphorylation/glutathione metabolism↑➡ Mitochondrial homeostasis↑	Maintenance of muscle cell function	[99]
Sarcopenia patients	PVT1↑	*c-Myc*	PVT1↑➡ *c-Myc*↓➡ *Bcl-2*↑➡ Mitochondrial dysfunction↑➡ Energy metabolism↓	Mitochondrial dysfunction, impaired energy metabolism	[100]
Human skeletal muscle cells and aged mice	SYISL↑	miR-103-3p, miR-205-5p, miR-23a-3p; PRC2 complex	SYISL↑➡Sponges miR-103-3p/miR-205-5p/miR-23a-3p ➡ *MuRF1/FoxO3a/Atrogin-1*↑ & Binds PRC2 ➡ *p21*/myogenin↓ ➡ Protein degradation↑ & Muscle regeneration↓	Activation of protein degradation, suppression of muscle regeneration	[101]
Skeletal muscle aging	PRKG1-AS1↑	*MyoD*, myogenin, MEF2C, *Myf5*	PRKG1-AS1↑➡*MyoD*/myogenin/MEF2C/*Myf5*↓➡Muscleproliferation/differentiation↓➡ Muscle atrophy↑	Accelerated muscle atrophy	[102]
Sarcopenia patients (skeletal muscle)	GPRC5D-AS1↓	*SLC7A11*	GPRC5D-AS1↓➡*SLC7A11* transcription/translation↓➡Glutathione synthesis↓ & Lipid peroxidation/ferroptosis↑➡ Antioxidant capacity↓	Increased ferroptosis, exacerbation of muscle atrophy	[103]
Aged mice and C2C12 cells	MALAT1↓	miR-34a-5p, TGF-β1	MALAT1↓➡ miR-34a-5p activation↑➡ SIRT1↓ & Cellular senescence↑; Also ➡ TGF-β1 activation↑➡ Muscle fibrosis↑	Muscle fiber atrophy, regenerative disorders	[104]
Type 2 diabetes skeletal muscle	TMEM9B-AS1↓	*MYC* (via IGF2BP1)	TMEM9B-AS1↓➡IGF2BP1 recruitment↓➡ MYC mRNA stability↓➡ MYC degradation↑➡ Ribosome production↓➡ Muscle protein synthesis↓	Loss of muscle mass and function	[106]
Muscle atrophy mice and C2C12 cells	circTmeff1↑	TDP-43	circTmeff1↑➡ Binds TDP-43 ➡ Mitochondrial aggregation of TDP-43↑➡ mtDNA release↑➡ cGAS/STING pathway activation↑➡ Protein degradation/apoptosis↑; Also encodes TMEFF1-339aa ➡ Muscle atrophy↑	Accelerated muscle atrophy	[110]
Muscle atrophy mice and C2C12 cells	circDdb1↑	eEF2	circDdb1↑➡ Encodes circDdb1-867aa ➡ Binds eEF2 & enhances Thr56 phosphorylation ➡ Protein synthesis↓; Also activates ubiquitin-proteasome/autophagy-lysosome pathways ➡ Protein degradation↑	Myofibrillar atrophy	[111]
Chicken skeletal muscle	circAGO3↑	miR-34b-5p, *TRAF3*	circAGO3↑➡ Sponges miR-34b-5p ➡ *TRAF3*↑➡ NF-κB signaling activation↑➡ Inflammation↑& Protein degradation pathways activation↑	Inflammatory atrophy, oxidative stress, apoptosis	[112]
Spinal muscular atrophy (SMA)	circRNA C2A-2B-3–4↓	Ribosome biogenesis, RNA metabolism genes	circRNA C2A-2B-3–4↓➡ Downregulation of ribosome biogenesis/RNA metabolism genes (e.g., *NAMPT*, *CELSR3*) & Upregulation of negative regulators (e.g., *GFRA1*, *SHTN1*, *CNTN1*) ➡ Protein synthesis imbalance	Muscle atrophy	[113]
SMA patients	circ4-2b-3↓	*SMN* mRNA	circ4-2b-3↓➡ Reduced interference with miRNAs/RBPs ➡ *SMN* mRNA splicing/stability↓➡ SMN protein deficiency↑➡ α-motor neuron degeneration↑	Muscle atrophy	[114]
Chicken skeletal muscle development	circCCDC91↓	miR-15 family (miR-15a, miR-15b-5p, miR-15c-5p)	circCCDC91↓➡ Reduced sponging of miR-15 family ➡ *IRS1* inhibition↑➡ *IGF1*-PI3K/AKT signaling↓➡ Myoblast proliferation/differentiation↓& Atrogin-1/*MuRF1*↑	Exacerbated sarcopenia (Note:↑ circCCDC91 is protective)	[115]

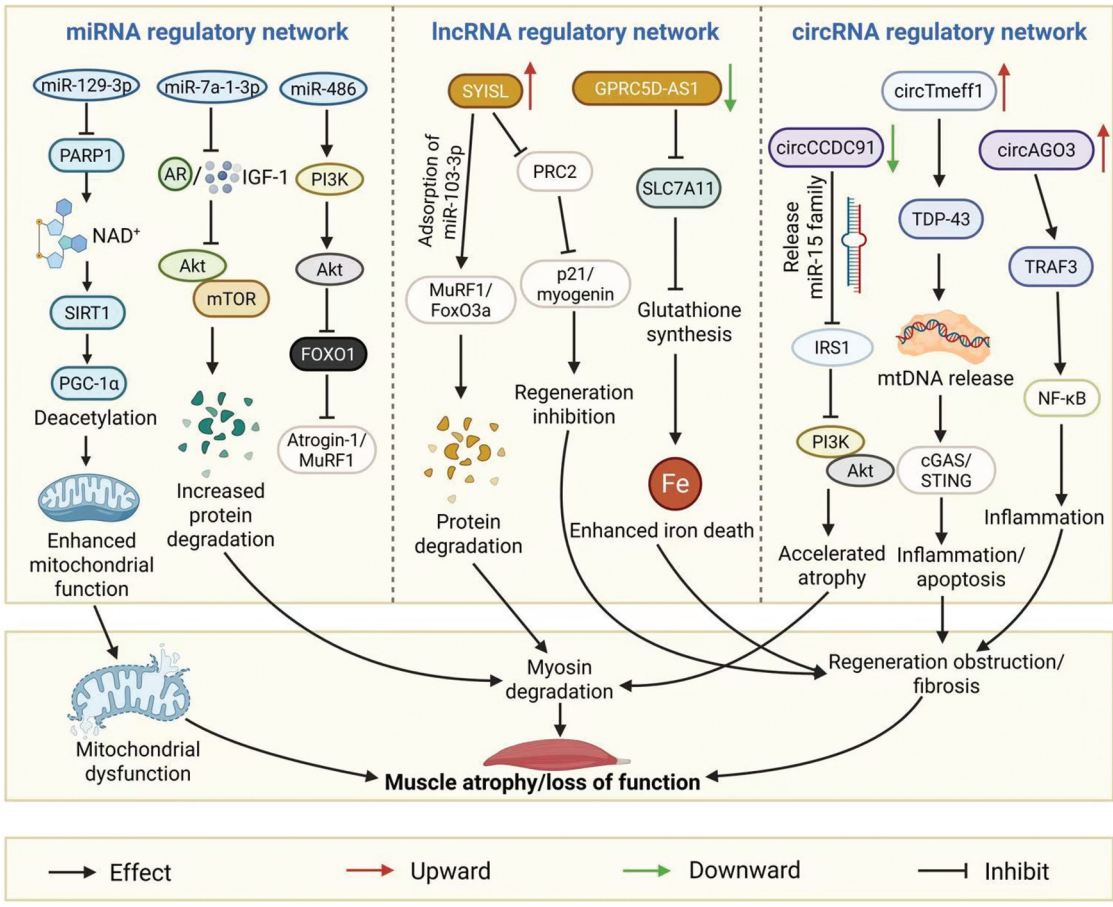

Figure 2. Regulatory networks of noncoding RNAs in sarcopenia Figure 2 is a conceptual diagram (created using BioRender.com) summarizing the reported regulatory roles of noncoding RNAs (miRNAs, lncRNAs, and circRNAs) in sarcopenia. Dysregulation of these ncRNAs is associated with impaired satellite cell differentiation, disrupted protein homeostasis, and mitochondrial dysfunction, which collectively contribute to muscle atrophy. The integrated network also illustrates the potential of specific ncRNAs as diagnostic biomarkers (e.g., circulating miR-451a) and therapeutic targets (e.g., miR-129-3p mimics or circCCDC91 restoration) for sarcopenia management.

Created in BioRender. Ding, F. (2025) https://BioRender.com/c18z1dk.

metabolism, and inflammatory signaling. This perspective extends etiological understanding beyond inherited genetic variation. DNA methylation regulates genes such as *FGF2*, *FoxO1*, and *MyoD*. Through these targets, DNA methylation influences satellite cell function, protein metabolic homeostasis, and mitochondrial biogenesis. Chromatin-remodeling pathways, mediated by BAF60c, HDACs, CARM1, and sirtuins, control myogenic gene accessibility, fiber-type transitions, and metabolic equilibrium. In parallel, ncRNAs form a multilayer regulatory network. This network modulates myocyte proliferation, differentiation, autophagy, and apoptosis via post-transcriptional and pathway-level mechanisms.

Clinical translation remains early. Blood-based methylation sites and circulating ncRNAs have been proposed as noninvasive biomarkers. However, the relationship between circulating epigenetic signatures and skeletal muscle – specific alterations is still poorly defined. Substantial interindividual variability further complicates interpretation and risk stratification. Key sources of variability include age, sex, physical activity, nutrition, systemic inflammation, and multimorbidity. Finally, limited longitudinal cohorts and a shortage of well-designed interventional trials constrain causal inference and delay validation of clinical utility.

Therapeutically, the reversibility of epigenetic modifications provides a conceptual rationale for targeted interventions; however, most candidate strategies remain in preclinical or early translational phases. Small-molecule epigenetic agents, including HDAC inhibitors and bromodomain and extra-terminal domain (BET) inhibitors, have demonstrated protective effects against muscle atrophy and mitochondrial dysfunction in experimental models, thereby providing a preliminary foundation for drug development [116]. Similarly, nucleic acid – based therapeutics delivered via exosomes – such as miRNAs and lncRNAs – have shown potential to modulate atrophy- and regeneration-related pathways in animal studies [117,118]. Emerging methylation-editing approaches, including targeted MyoD demethylation and clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9)-based systems, have further illustrated the feasibility of precise epigenetic modulation in skeletal muscle regeneration [13]. Nevertheless, issues related to delivery efficiency, tissue specificity, long-term safety, and off-target effects remain unresolved, and robust clinical evidence is currently lacking.

Taken together, epigenetic research holds promise for biomarker development and mechanism-based therapies in

sarcopenia, but clinical adoption requires cautious interpretation and rigorous validation. Future work should prioritize multi-omics integration, standardized biomarker pipelines, longitudinal cohorts, and randomized trials to translate experimental findings into practice. Epigenetic approaches are most likely to complement rather than replace exercise and nutritional interventions, supporting a stratified, mechanism-informed model of sarcopenia care.

7. Future perspective

Over the next 5–10 years, research is expected to focus on several key areas.

Firstly, the discovery and clinical validation of epigenetic biomarkers are expected to remain central research priorities. Although several promising blood-based biomarkers have been identified, their clinical utility remains supported by evidence from large-scale, multicenter cohorts with well-defined phenotypes and long-term longitudinal follow-up. Future work should prioritize standardizing analytical platforms and fostering stronger interdisciplinary collaboration. Integrating epigenetic markers with conventional muscle function assessments – such as muscle mass, handgrip strength, and gait speed will be essential to enhance their value for early detection, risk stratification, and therapeutic monitoring.

The rapid evolution of single-cell and spatial epigenomics, combined with multi-omics integration strategies, is poised to significantly refine the mechanistic understanding of sarcopenia. Compared with bulk-tissue approaches, technologies such as single-cell ATAC-seq, single-cell methylome profiling, and spatial epigenetic transcriptomics enable the identification of cell – type – specific epigenetic alterations, clarify dynamic cellular state transitions, and delineate interactions within the local microenvironment. When coupled with proteomic and metabolomic analyses, these tools will facilitate the precise mapping of critical regulatory nodes and the development of a comprehensive catalog of actionable therapeutic targets.

In parallel, epigenetic-based therapeutics, including small-molecule agents such as sirtuin activators and nucleic acid therapeutics such as miRNA/lncRNA modulators, are expected to advance into more rigorous preclinical evaluation and early-phase clinical testing. Concurrent advances in delivery technologies and the exceptional engineering of exosomes are anticipated to improve tissue specificity, enhance delivery efficiency, and strengthen the overall safety profile of these interventions, thereby supporting their translational viability.

Integrating lifestyle interventions, such as exercise and nutrition, with epigenetic-based approaches is a promising direction. Exercise and diet can reshape the epigenetic landscape of skeletal muscle and may synergize with pharmacological strategies to support mitochondrial function and protein homeostasis. Future trials could use epigenetic biomarkers as intermediate endpoints to guide personalized interventions and evaluate repurposed epigenetic drugs, improving feasibility and accelerating translation.

As evidence accumulates, continued epigenetic research in sarcopenia is expected to strengthen early detection and enable more targeted treatment and prevention, ultimately improving quality of life.

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Author contributions

Yuan Zhao: Conceptualization, Writing – Review & Editing, Supervision, Funding Acquisition; Shiyan Gu: Conceptualization, Writing – Review&Editing; Mei Wu: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Visualization; Han Lu: Writing – Review & Editing, Visualization; Yilin Yang: Writing – Review & Editing, Visualization; Yaolei Cha: Writing – Review & Editing, Visualization; Qing Yang: Writing – Review & Editing, Visualization; Lijie Yang: Resources, Visualization; Zhexi Xiao: Resources, Visualization. All authors approved the final manuscript submission and agreed to be responsible for all aspects of the work.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Kirk B, Cawthon PM, Arai H, et al. Global Leadership Initiative in Sarcopenia (GLIS) Group. The conceptual definition of sarcopenia: delphi consensus from the global leadership initiative in sarcopenia (GLIS). Age Ageing. 2024;53(3):afae052. doi: 10.1093/ageing/afae052
2. Zhang FM, Wu HF, Shi HP, et al. Sarcopenia and malignancies: epidemiology, clinical classification and implications. Ageing Res Rev. 2023;91:102057. doi: 10.1016/j.arr.2023.102057
3. Damluji AA, Alfaraidhy M, AlHajri N, et al. Sarcopenia and cardiovascular diseases. Circulation. 2023;147(20):1534–1553. doi: 10.1161/CIRCULATIONAHA.123.064071
4. Hashimoto Y, Takahashi F, Okamura T, et al. Diet, exercise, and pharmacotherapy for sarcopenia in people with diabetes. Metabolism. 2023;144:155585. doi: 10.1016/j.metabol.2023.155585

5. Polyzos SA, Vachliotis ID, Mantzoros CS. Sarcopenia, sarcopenic obesity and nonalcoholic fatty liver disease. Metabolism. 2023;147:155676. doi: 10.1016/j.metabol.2023.155676
6. Zhang K, Zheng X, Ma T. Association of possible sarcopenia, sarcopenia and sarcopenic obesity with multimorbidity among middle-aged and older adults: findings from the China health and retirement longitudinal study. Arch Public Health. 2025;83(1):77. doi: 10.1186/s13690-025-01538-y
7. Sayer AA, Cooper R, Arai H, et al. Sarcopenia. Nat Rev Dis Primers. 2024;10(1):68. doi: 10.1038/s41572-024-00550-w
8. Kirk B, Lombardi G, Duque G. Bone and muscle crosstalk in ageing and disease. Nat Rev Endocrinol. 2025;21(6):375–390. doi: 10.1038/s41574-025-01088-x
9. Tarantino U, Greggi C, Visconti VV, et al. Sarcopenia and bone health: new acquisitions for a firm liaison. Ther Adv Musculoskelet Dis. 2022;14:1759720X221138354. doi: 10.1177/1759720X221138354
10. Du J, Wu Q, Bae EJ. Epigenetics of skeletal muscle atrophy. Int J Mol Sci. 2024;25(15):8362. doi: 10.3390/ijms25158362

•• **A foundational review summarizing the core epigenetic mechanisms regulating skeletal muscle atrophy, directly supporting this study's mechanistic framework.**

11. Smith JAB, Murach KA, Dyar KA, et al. Exercise metabolism and adaptation in skeletal muscle. Nat Rev Mol Cell Biol. 2023;24(9):607–632. doi: 10.1038/s41580-023-00606-x
12. Clynes MA, Gregson CL, Bruyère O, et al. Osteosarcopenia: where osteoporosis and sarcopenia collide. Rheumatol (Oxford). 2021;60(2):529–537. doi: 10.1093/rheumatology/keaa755
13. Nusrat S, Din RU, Tariq MA, et al. Epigenetic dysregulation and osteocyte senescence: convergent drivers of osteosarcopenia in aging bone and muscle. Aging Dis. 2025. doi: 10.14336/AD.2025.0370
14. Li Y, Hu M, Xie J, et al. Dysregulation of histone modifications in bone marrow mesenchymal stem cells during skeletal ageing: roles and therapeutic prospects. Stem Cell Res Ther. 2023;14(1):166. doi: 10.1186/s13287-023-03393-6
15. Zhang T, Neunaber C, Ye W, et al. Aging influences fracture healing on the cellular level and alters systemic RANKL and OPG concentrations in a murine model. Adv Biol (Weinh). 2024;8(11):e2300653. doi: 10.1002/adbi.202300653
16. Choi MC, Ryu S, Hao R, et al. HDAC4 promotes Pax7-dependent satellite cell activation and muscle regeneration. EMBO Rep. 2014;15(11):1175–1183. doi: 10.15252/embr.201439195
17. Huang Z, Hu L, Liu Z, et al. The functions and regulatory mechanisms of histone modifications in skeletal muscle development and disease. Int J Mol Sci. 2025;26(8):3644. doi: 10.3390/ijms26083644
18. Wu J, Gulati S, Teague AM, et al. AMPK regulates DNA methylation of PGC-1α and myogenic differentiation in human mesenchymal stem cells. Stem Cells Dev. 2023;32(5–6):131–139. doi: 10.1089/scd.2022.0226
19. Kirk B, Feehan J, Lombardi G, et al. Muscle, bone, and fat crosstalk: the biological role of myokines, osteokines, and adipokines. Curr Osteoporos Rep. 2020;18(4):388–400. doi: 10.1007/s11914-020-00599-y
20. Cui Y, Yi Q, Sun W, et al. Molecular basis and therapeutic potential of myostatin on bone formation and metabolism in orthopedic disease. Biofactors. 2023;49(1):21–31. doi: 10.1002/biof.1675
21. Li H, Liu G, Wang B, et al. Exosomes and microRNAs as mediators of the exercise. Eur J Med Res. 2025;30(1):38. doi: 10.1186/s40001-025-02273-4
22. Zykovich A, Hubbard A, Flynn JM, et al. Genome-wide DNA methylation changes with age in disease-free human skeletal muscle. Aging Cell. 2014;13(2):360–366. doi: 10.1111/acel.12180
23. Celik D, Campisi M, Cannella L, et al. The effect of low birth weight as an intrauterine exposure on the early onset of sarcopenia through possible molecular pathways. J Cachexia Sarcopenia Muscle. 2024;15(3):770–780. doi: 10.1002/jcsm.13455
24. Xu Z, Shi J, Chen Q, et al. Regulation of de novo and maintenance DNA methylation by DNA methyltransferases in postimplantation embryos. J Biol Chem. 2025;301(1):107990. doi: 10.1016/j.jbc.2024.107990
25. Wu Z, Zhang W, Qu J, et al. Emerging epigenetic insights into aging mechanisms and interventions. Trends Pharmacol Sci. 2024;45(2):157–172. doi: 10.1016/j.tips.2023.12.002
26. Higham J, Kerr L, Zhang Q, et al. Local CpG density affects the trajectory and variance of age-associated DNA methylation changes. Genome Biol. 2022;23(1):216. doi: 10.1186/s13059-022-02787-8
27. Gim JA, Lee SY, Kim SC, et al. Relationship between DNA methylation changes and skeletal muscle mass. BMC Genom Data. 2023;24(1):48. doi: 10.1186/s12863-023-01152-3
28. Liang W, Xu F, Li L, et al. Epigenetic control of skeletal muscle atrophy. Cell Mol Biol Lett. 2024;29(1):99. doi: 10.1186/s11658-024-00618-1

•• **Offers in-depth mechanistic insights into chromatin remodeling and methylation pathways underlying muscle atrophy, highly relevant to the article's central arguments.**

29. Oyabu M, Ohira Y, Fujita M, et al. Dnmt3a overexpression disrupts skeletal muscle homeostasis, promotes an aging-like phenotype, and reduces metabolic elasticity. iScience. 2025;28(4). doi: 10.1016/j.isci.2025.112144
30. Foreman NA, Hesse AS, Ji LL. Redox signaling and sarcopenia: searching for the primary suspect. Int J Mol Sci. 2021;22(16):9045. doi: 10.3390/ijms22169045
31. Anagnostou D, Theodorakis N, Hitas C, et al. Sarcopenia and cardiogeriatrics: the links between skeletal muscle decline and cardiovascular aging. Nutrients. 2025;17(2):282. doi: 10.3390/nu17020282
32. Li J, Wang Z, Li C, et al. Impact of exercise and aging on mitochondrial homeostasis in skeletal muscle: roles of ROS and epigenetics. Cells. 2022;11(13):2086. doi: 10.3390/cells11132086
33. Sharma AR, Chatterjee S, Lee YH, et al. Targeting crosstalk of signaling pathways among muscles-bone-adipose tissue: a promising therapeutic approach for sarcopenia. Aging Dis. 2024;15(4):1619–1645. doi: 10.14336/AD.2023.00903
34. Li Q, Liu Q, Lin Z, et al. Hypomethylation in promoters of pgc-1α involved in exercise-driven skeletal muscular alterations in old age. Open Life Sci. 2024;19(1):20220959. doi: 10.1515/biol-2022-0959
35. Krämer AI, Handschin C. How epigenetic modifications drive the expression and mediate the action of PGC-1α in the regulation of metabolism. Int J Mol Sci. 2019;20(21):5449. doi: 10.3390/ijms20215449
36. Gorski PP, Turner DC, Iraki J, et al. Human skeletal muscle methylome after low-carbohydrate energy-balanced exercise. Am J Physiol Endocrinol Metab. 2023;324(5):E437–E448. doi: 10.1152/ajpendo.00029.2023
37. Maehara H, Kokaji T, Hatano A, et al. DNA hypomethylation characterizes genes encoding tissue-dominant functional proteins in liver and skeletal muscle. Sci Rep. 2023;13(1):19118. doi: 10.1038/s41598-023-46393-5
38. Dogan B, Kaan D, Ulger H. The effect of growth factors on induction of mesenchymal stem cell to the skeletal muscle cells. Bratisl Lek Listy. 2020;121(12):853–857. doi: 10.4149/BLL_2020_140
39. Graham ZA, DeBerry JJ, Cardozo CP, et al. A 50 kdyne contusion spinal cord injury with or without the drug ss-31 was not associated with major changes in muscle mass or gene expression 14 d after injury in young male mice. Physiol Rep. 2021;9(4):e14751. doi: 10.14814/phy2.14751
40. He L, Khanal P, Morse CI, et al. Differentially methylated gene patterns between age-matched sarcopenic and nonsarcopenic women. J Cachexia Sarcopenia Muscle. 2019;10(6):1295–1306. doi: 10.1002/jcsm.12478
41. Li JW, Shen ZK, Lin YS, et al. DNA methylation of skeletal muscle function-related secretary factors identifies fgf2 as a potential biomarker for sarcopenia. J Cachexia Sarcopenia Muscle. 2024;15(3):1209–1217. doi: 10.1002/jcsm.13472

• **Identifies *FGF2* as a methylation-regulated biomarker, directly supporting the biomarker section of this study.**

42. Mattei AL, Bailly N, Meissner A. DNA methylation: a historical perspective. Trends Genet. 2022;38(7):676–707. doi: 10.1016/j.tig.2022.03.010

43. Fujii I, Kinoshita R, Akiyama H, et al. Discovery of fibroblast growth factor 2-derived peptides for enhancing mice skeletal muscle satellite cell proliferation. Biotechnol J. 2024;19(8):e2400278. doi: 10.1002/biot.202400278
44. Wang H, Bai R, Wang Y, et al. The multifaceted function of FoxO1 in pancreatic β-cell dysfunction and insulin resistance: therapeutic potential for type 2 diabetes. Life Sci. 2025;364:123384. doi: 10.1016/j.lfs.2025.123384
45. Jaiswal N, Gavin M, Loro E, et al. AKT controls protein synthesis and oxidative metabolism via combined mTORC1 and FOXO1 signaling to govern muscle physiology. J Cachexia Sarcopenia Muscle. 2022;13(1):495–514. doi: 10.1002/jcsm.12846
46. Kim KH, Oprescu SN, Snyder MM, et al. PRMT5 mediates FoxO1 methylation and subcellular localization to regulate lipophagy in myogenic progenitors. Cell Rep. 2023;42(11):113329. doi: 10.1016/j.celrep.2023.113329
47. Shi P, Ruan Y, Liu W, et al. Analysis of promoter methylation of the bovine FOXO1 gene and its effect on proliferation and differentiation of myoblasts. Animals (Basel). 2023;13(2):319. doi: 10.3390/ani13020319
48. Tsuji R, Hayashi T, Takahashi S, et al. The multifaceted role of MyoD in adult skeletal muscle: homeostasis, regeneration, and diseases. Am J Physiol Cell Physiol. 2025;329(1):C200–C212. doi: 10.1152/ajpcell.00334.2025
49. Wei D, Feng L, Zhang W, et al. Corrigendum to "Characterization of the promoter region of bovine SIX4: roles of E-box and MyoD in the regulation of basal transcription". Biochem Biophys Res Commun. 2022;612:196–197. doi: 10.1016/j.bbrc.2022.04.124
50. Vicente-García C, Hernández-Camacho JD, Carvajal JJ. Regulation of myogenic gene expression. Exp Cell Res. 2022;419(1):113299. doi: 10.1016/j.yexcr.2022.113299
51. Turner DC, Gorski PP, Maasar MF, et al. DNA methylation across the genome in aged human skeletal muscle tissue and muscle-derived cells: the role of HOX genes and physical activity. Sci Rep. 2020;10(1):15360. doi: 10.1038/s41598-020-72730-z
52. Baribault C, Ehrlich KC, Ponnaluri VKC, et al. Developmentally linked human DNA hypermethylation is associated with downmodulation, repression, and upregulation of transcription. Epigenetics. 2018;13(3):275–289. doi: 10.1080/15592294.2018.1445900
53. Sen S, Lacey M, Baribault C, et al. The myoblast methylome: multiple types of associations with chromatin and transcription. Epigenetics. 2025;20(1):2508251. doi: 10.1080/15592294.2025.2508251
54. Kim I, Ghosh A, Bundschuh N, et al. Integrative molecular roadmap for direct conversion of fibroblasts into myocytes and myogenic progenitor cells. Sci Adv. 2022;8(14):eabj4928. doi: 10.1126/sciadv.abj4928
55. Yagi M, Ji F, Charlton J, et al. Dissecting dual roles of MyoD during lineage conversion to mature myocytes and myogenic stem cells. Genes Dev. 2021;35(17–18):1209–1228. doi: 10.1101/gad.348678.121
56. Cai Z, Jia X, Liu M, et al. Epigenome-wide DNA methylation study of whole blood in patients with sporadic amyotrophic lateral sclerosis. Chin Med J (Engl). 2022;135(12):1466–1473. doi: 10.1097/CM9.0000000000002090
57. Murach KA, Englund DA, Chambers TL, et al. A satellite cell-dependent epigenetic fingerprint in skeletal muscle identity genes after lifelong physical activity. FASEB J. 2025;39(5):e70435. doi: 10.1096/fj.202500177R
- **Provides evidence that physical activity induces lasting epigenetic signatures in muscle satellite cells, supporting the discussion on exercise–epigenetic interactions.**
58. Voisin S, Jacques M, Landen S, et al. Meta-analysis of genome-wide DNA methylation and integrative omics of age in human skeletal muscle. J Cachexia Sarcopenia Muscle. 2021;12(4):1064–1078. doi: 10.1002/jcsm.12741
59. Li H, Liang M, Huang G, et al. Chromatin remodeling factor 28 and heat shock factor a2 activate binding immunoglobulin protein 3 under heat stress. Plant Physiol. 2025;197(4):kiaf090. doi: 10.1093/plphys/kiaf090
60. Li C, Sun Y. Investigation of chromatin remodeling-related biomarkers and associated molecular mechanism in pulpitis. Gene. 2025;934:149016. doi: 10.1016/j.gene.2024.149016
61. Morrison AJ. Chromatin-remodeling links metabolic signaling to gene expression. Mol Metab. 2020;38:100973. doi: 10.1016/j.molmet.2020.100973
62. Cenik BK, Shilatifard A. COMPASS and SWI/SNF complexes in development and disease. Nat Rev Genet. 2021;22(1):38–58. doi: 10.1038/s41576-020-0278-0
63. Han S, Jin L, Peng W, et al. Baf60c in skeletal muscle regulates adipose tissue thermogenesis via musclin-mediated endocrine signaling. Life Metab. 2025;4(4):loaf015. doi: 10.1093/lifemeta/loaf015
- **Demonstrates BAF60c as a key chromatin-remodeling factor influencing muscle metabolic function, related to epigenetic regulation in sarcopenia.**
64. Jin L, Han S, Lv X, et al. The muscle-enriched myokine musclin impairs beige fat thermogenesis and systemic energy homeostasis via Tfr1/PKA signaling in male mice. Nat Commun. 2023;14(1):4257. doi: 10.1038/s41467-023-39710-z
65. Liu Y, Fan Z, Zhai Y, et al. The multifaceted roles of BAF60 subunits in muscle: regulation of differentiation, reprogramming, and metabolic homeostasis. Front Cell Dev Biol. 2025;13:1594423. doi: 10.3389/fcell.2025.1594423
66. Sahu RK, Dhakshnamoorthy J, Jain S, et al. Nucleosome remodeler exclusion by histone deacetylation enforces heterochromatic silencing and epigenetic inheritance. Mol Cell. 2024;84(17):3175–3191. doi: 10.1016/j.molcel.2024.07.006
67. Cai L, Shi L, Peng Z, et al. Aging of skeletal muscle extracellular matrix and mitochondria: finding a potential link. Ann Med. 2023;55(2):2240707. doi: 10.1080/07853890.2023.2240707
68. Tu C, Wang SC, Dai MX, et al. Accumulation of advanced oxidative protein products exacerbate satellite glial cells activation and neuropathic pain. Mol Med. 2025;31(1):25. doi: 10.1186/s10020-025-01076-x
69. Xu J, Li X, Chen W, et al. Myofiber baf60c controls muscle regeneration by modulating dkk3-mediated paracrine signaling. J Exp Med. 2023;220(9):e20221123. doi: 10.1084/jem.20221123
70. Reyes AA, Marcum RD, He Y. Structure and function of chromatin remodelers. J Mol Biol. 2021;433(14):166929. doi: 10.1016/j.jmb.2021.166929
71. Moreno-Justicia R, Van der Stede T, Stocks B, et al. Human skeletal muscle fiber heterogeneity beyond myosin heavy chains. Nat Commun. 2025;16(1):1764. doi: 10.1038/s41467-025-56896-6
72. Hernández-Hernández O, Ávila-Avilés RD, Hernández-Hernández JM. Chromatin landscape during skeletal muscle differentiation. Front Genet. 2020;11:578712. doi: 10.3389/fgene.2020.578712
73. Tan B, Hong L, Xiao L, et al. Rewiring of 3D chromatin topology orchestrates transcriptional reprogramming in muscle fiber-type specification and transformation. Nat Commun. 2025;16(1):5833. doi: 10.1038/s41467-025-60866-3
74. Baar K. Epigenetic control of skeletal muscle fiber type. Acta Physiol (Oxf). 2010;199(4):477–487. doi: 10.1111/j.1748-1716.2010.02121.x
75. Sincennes MC, Brun CE, Rudnicki MA. Concise review: epigenetic regulation of myogenesis in health and disease. Stem Cells Transl Med. 2016;5(3):282–290. doi: 10.5966/sctm.2015-0266
76. Kamarulzaman NT, Makpol S. The link between mitochondria and sarcopenia. J Physiol Biochem. 2025;81(1):1–20. doi: 10.1007/s13105-024-01062-7
77. Hou GZ, Guo Q, Han PP. Autophagy activation and mitochondrial quality control in sarcopenia. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2022;44(4):709–716. doi: 10.3881/j.issn.1000-503X.13753
78. Tian X, Lou S, Shi R. From mitochondria to sarcopenia: role of 17β-estradiol and testosterone. Front Endocrinol (Lausanne). 2023;14:1156583. doi: 10.3389/fendo.2023.1156583
79. Wiedmer P, Jung T, Castro JP, et al. Sarcopenia-molecular mechanisms and open questions. Aging Res Rev. 2021;65:101200. doi: 10.1016/j.arr.2020.101200
80. Chen X, Huang MF, Fan DM, et al. CARM1 hypermethylates the NuRD chromatin remodeling complex to promote cell cycle gene expression and breast cancer development. Nucleic Acids Res. 2024;52(12):6811–6829. doi: 10.1093/nar/gkae329
81. Stouth DW, van Lieshout TL, Mikhail AI, et al. Carm1 drives mitophagy and autophagy flux during fasting-induced skeletal muscle atrophy.

Autophagy. 2024;20(6):1247–1269. doi: 10.1080/15548627.2023.2288528
82. Liu H, Wang S, Wang J, et al. Energy metabolism in health and diseases. Signal Transduct Target Ther. 2025;10(1):69. doi: 10.1038/s41392-025-02141-x
83. Zhang Z, Guo Q, Yang Z, et al. Bifidobacterium adolescentis-derived nicotinic acid improves host skeletal muscle mitochondrial function to ameliorate sarcopenia. Cell Rep. 2025;44(2):115265. doi: 10.1016/j.celrep.2025.115265
84. Song G, Park J, Jung Y, et al. Regulating sirtuin 3-mediated mitochondrial dynamics through vanillic acid improves muscle atrophy in cancer-induced cachexia. Commun Biol. 2025;8(1):585. doi: 10.1038/s42003-025-07770-0
85. Chen G, Zou J, He Q, et al. The role of non-coding RNAs in regulating cachexia muscle atrophy. Cells. 2024;13(19):1620. doi: 10.3390/cells13191620
• **Offers mechanistic insights into non-coding RNA–mediated regulation of muscle atrophy, relevant to RNA-based therapeutic strategies.**
86. Falduti A, Giovinazzo A, Lo Feudo E, et al. The role of non-coding RNAs in ALS. Genes (Basel). 2025;16(6):623. doi: 10.3390/genes16060623
87. Alizadeh M, Ghasemi H, Bazhan D, et al. MicroRNAs in disease states. Clin Chim Acta. 2025;569:120187. doi: 10.1016/j.cca.2025.120187
88. Sannicandro AJ, Soriano-Arroquia A, Goljanek-Whysall K. Micro(RNA)-managing muscle wasting. J Appl Physiol (1985). 2019;127(2):619–632. doi: 10.1152/japplphysiol.00961
89. Fochi S, Giuriato G, De Simone T, et al. Regulation of MicroRNAs in satellite cell renewal, muscle function, sarcopenia and the role of exercise. Int J Mol Sci. 2020;21(18):6732. doi: 10.3390/ijms21186732
90. Mancuso R, Citterio LA, Agostini S, et al. Circulatory titin and miR-451a are possible sarcopenia biomarkers in elderly people. Front Aging. 2025;6:1587438. doi: 10.3389/fragi.2025.1587438
91. Kim H, Lee YY, Kim VN. The biogenesis and regulation of animal microRNAs. Nat Rev Mol Cell Biol. 2025;26(4):276–296. doi: 10.1038/s41580-024-00805-0
92. Liang J, Zhang H, Zeng Z, et al. MicroRNA profiling of different exercise interventions for alleviating skeletal muscle atrophy in naturally aging rats. J Cachexia Sarcopenia Muscle. 2023;14(1):356–368. doi: 10.1002/jcsm.13137
93. Qiu D, Zhang Y, Ni P, et al. Muscle-enriched microRNA-486-mediated regulation of muscular atrophy and exercise. J Physiol Biochem. 2024;80(4):795–809. doi: 10.1007/s13105-024-01043-w
94. Shin YJ, Yang JW, Jeong H, et al. ExermiR-129-3p enhances muscle function by improving mitochondrial activity through PARP1 inhibition. J Cachexia Sarcopenia Muscle. 2025;16(2):e13823. doi: 10.1002/jcsm.13823
95. An L, Wang Y. Potential roles of miRNA-1245a regulatory networks in sarcopenia. Int J Gen Med. 2021;14:6807–6813. doi: 10.2147/IJGM.S334501
96. Zhu X, Dong W, Zhang M. lncRNA ac004943.2 regulates mir-135a-5p and ptk2/p13k axis to promote laryngeal squamous cell carcinoma progression. J Cell Commun Signal. 2024;18(1):e12016. doi: 10.1002/ccs3.12016
97. Herman AB, Tsitsipatis D, Gorospe M. Integrated lncRNA function upon genomic and epigenomic regulation. Mol Cell. 2022;82(12):2252–2266. doi: 10.1016/j.molcel.2022.05.027
98. Chiu HS, Somvanshi S, Chen TW, et al. Illuminating lncRNA function through target prediction. Methods Mol Biol. 2021;2372:263–295. doi: 10.1007/978-1-0716-1697-0_22
99. Yu J, Loh K, Yang HQ, et al. The whole-transcriptome landscape of diabetes-related sarcopenia reveals the specific function of novel lncRNA Gm20743. Commun Biol. 2022;5(1):774. doi: 10.1038/s42003-022-03728-8
100. Aparicio P, López-Royo T, Navarrete-Villanueva D, et al. Serum lncRnas NEAT1, PVT1 and H19 as novel biomarkers for sarcopenia diagnosis and treatment response. Noncoding RNA Res. 2025;14:166–176. doi: 10.1016/j.ncrna.2025.06.003
101. Zhang Y, Wang T, Wang Z, et al. Functions and therapeutic potentials of long noncoding RNA in skeletal muscle atrophy and dystrophy. J Cachexia Sarcopenia Muscle. 2025;16(2):e13747. doi: 10.1002/jcsm.13747
102. Zheng Y, Liu T, Li Q, et al. Integrated analysis of long noncoding RNAs (lncRNAs) and mRNA expression profiles identifies lncRNA PRKG1-AS1 playing important roles in skeletal muscle aging. Aging (Albany NY). 2021;13(11):15044–15060. doi: 10.18632/aging.203067
103. Gong W, Wang Y, Li Q, et al. Regulation of SLC7A11 by lncRNA GPRC5D-AS1 mediates ferroptosis in skeletal muscle: mechanistic exploration of sarcopenia. Front Mol Biosci. 2025;12:1557218. doi: 10.3389/fmolb.2025.1557218
104. Ruan L, Mendhe B, Parker E, et al. Long noncoding RNA MALAT1 is depleted with age in skeletal muscle in vivo and MALAT1 silencing increases expression of TGF-β1 in vitro. Front Physiol. 2022;12:742004. doi: 10.3389/fphys.2021.742004
105. Chaillou T, Montiel-Rojas D. Does the blunted stimulation of skeletal muscle protein synthesis by aging in response to mechanical load result from impaired ribosome biogenesis? Front Aging. 2023;4:1171850. doi: 10.3389/fragi.2023.1171850
106. Sen I, Smith JAB, Caria E, et al. Downregulation of human-specific lncRNA TMEM9B-AS1 in skeletal muscle of people with type 2 diabetes affects ribosomal biogenesis. Sci Adv. 2025;11(28):eads4371. doi: 10.1126/sciadv.ads4371
107. Hashemi M, Khosroshahi EM, Daneii P, et al. Emerging roles of circRNA-miRNA networks in cancer development and therapeutic response. Noncoding RNA Res. 2024;10:98–115. doi: 10.1016/j.ncrna.2024.09.006
108. Chen LL. The expanding regulatory mechanisms and cellular functions of circular rnas. Nat Rev Mol Cell Biol. 2020;21(8):475–490. doi: 10.1038/s41580-020-0243-y
109. Yi Q, Feng J, Lan W, et al. CircRNA and lncRNA-encoded peptide in diseases, an update review. Mol Cancer. 2024;23(1):214. doi: 10.1186/s12943-024-02131-7
110. Chen R, Yang T, Jin B, et al. CircTmeff1 promotes muscle atrophy by interacting with TDP-43 and encoding a novel TMEFF1-339aa protein. Adv Sci (Weinh). 2023;10(17):e2206732. doi: 10.1002/advs.202206732
111. Zhu X, Yang T, Zheng Y, et al. EIF4A3-induced circular RNA circDdb1 promotes muscle atrophy through encoding a novel protein circDdb1-867aa. Adv Sci (Weinh). 2024;11(45):e2406986. doi: 10.1002/advs.202406986
112. Zhao X, Tang S, Lei Z, et al. CircAGO3 facilitates NF-κB pathway-mediated inflammatory atrophy in chicken skeletal muscle via the miR-34b-5p/TRAF3 axis. Int J Biol Macromol. 2024;283(Pt 3):137614. doi: 10.1016/j.ijbiomac.2024.137614
113. Luo D, Ottesen EW, Lee JH, et al. Transcriptome-and proteome-wide effects of a circular RNA encompassing four early exons of the spinal muscular atrophy genes. Sci Rep. 2024;14(1):10442. doi: 10.1038/s41598-024-60593-7
114. Guerra M, Marini A, Pagliarini V, et al. High expression of SMN circ4-2b-3 in SMA I children treated with Nusinersen is associated with improved motor outcomes. Mol Neurobiol. 2025;62(5):5640–5649. doi: 10.1007/s12035-024-04605-7
115. Zhao J, Zhao X, Shen X, et al. CircCCDC91 regulates chicken skeletal muscle development by sponging miR-15 family by activating IGF1-PI3K/AKT signaling pathway. Poult Sci. 2022;101(5):101803. doi: 10.1016/j.psj.2022.101803
116. Nevi L, Pöllänen N, Penna F, et al. Targeting epigenetic regulators with HDAC and BET inhibitors to modulate muscle wasting. Int J Mol Sci. 2023;24(22):16404. doi: 10.3390/ijms242216404
•• **High-value reference supporting pharmacological interventions targeting epigenetic regulators, directly used in the therapeutic prospects section.**
117. Gao Y, Liu D, Xiao Q, et al. Exploration of pathogenesis and cutting-edge treatment strategies of sarcopenia: a narrative review. Clin Interv Aging. 2025;20:659–684. doi: 10.2147/CIA.S517833
118. Luo X, Wang J, Ju Q, et al. Molecular mechanisms and potential interventions during aging-associated sarcopenia. Mech Ageing Dev. 2025;223:112020. doi: 10.1016/j.mad.2024.112020