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Review

Genomic and Epigenomic Landscapes of Sarcopenia: From Molecular Etiology to Precision Interventions

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ABSTRACT: Sarcopenia-the age-related loss of skeletal muscle mass and strength-is a major contributor to frailty, disability, and mortality in the elderly. Once considered a physiological consequence of aging, sarcopenia is now recognized as a complex multifactorial syndrome driven by intricate interactions between genetic predispositions, epigenetic regulation, environmental exposures, and lifestyle factors. Recent advances in high-throughput genomics and epigenomics have transformed our understanding of its molecular underpinnings, revealing key genes, signaling pathways, and regulatory networks that govern muscle homeostasis, regeneration, and degeneration. Furthermore, epigenetic alterations such as DNA methylation, histone modifications, and non-coding RNA networks act as critical modulators of muscle aging, bridging genetic risk with environmental and metabolic influences. Here, we review current knowledge of the genomic and epigenomic landscapes of sarcopenia, discuss how they intersect with cellular and systemic processes, and explore how these insights are paving the way for precision diagnostics, risk prediction, and targeted therapeutic interventions.

Keywords: Sarcopenia, Skeletal muscle aging, Genomics, Epigenomics, DNA methylation, Non-coding RNA, Multi-omics, Precision medicine

1. Introduction

Sarcopenia is a progressive, systemic, and multifactorial syndrome characterized by the age-related decline in skeletal muscle mass, strength, and physical performance. As one of the most prevalent manifestations of biological aging, it affects approximately 10-30% of individuals over the age of 60 and nearly half of those above 80, imposing a substantial burden on public health systems worldwide. Beyond its direct impact on mobility and independence, sarcopenia is a major contributor to frailty, falls, hospitalization, metabolic disorders, and mortality. The World Health Organization has recognized sarcopenia as a distinct disease entity (ICD-10-CM code M62.84) [1], underscoring its clinical significance and the urgent need for effective interventions in aging societies. Traditionally, sarcopenia was considered an inevitable consequence of aging, primarily attributed to physical inactivity, hormonal decline, nutritional deficiencies, and neuromuscular degeneration. However, this reductionist view is increasingly being replaced by a more nuanced understanding that recognizes sarcopenia as the product of a complex biological interplay among genetic predispositions, epigenetic regulation, metabolic reprogramming, chronic inflammation, and environmental influences [2]. These factors collectively shape the muscle's capacity for protein synthesis and degradation, mitochondrial function, regenerative potential, and stress resilience [3-5].

At the cellular level, sarcopenia is associated with a multitude of pathophysiological changes, including satellite cell exhaustion, impaired autophagy,

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mitochondrial dysfunction, increased oxidative stress, and chronic low-grade inflammation-a phenomenon often described as "inflammaging." These processes are not isolated but are tightly regulated by genetic programs and epigenetic modifications that orchestrate transcriptional networks throughout the lifespan [6]. Such molecular changes contribute to the progressive remodeling of muscle tissue, affecting not only muscle fiber size and composition but also systemic metabolic homeostasis and inter-organ communication. The advent of high-throughput "omics" technologies has revolutionized our understanding of the molecular basis of sarcopenia. Genome-wide association studies (GWAS) have identified dozens of loci linked to muscle mass, fiber type distribution, and regenerative capacity, highlighting the role of genes involved in anabolic signaling, proteostasis, mitochondrial dynamics, and inflammatory pathways. Complementary approaches such as transcriptomics, single-cell sequencing, and next-generation sequencing (NGS) have further delineated the transcriptional and genetic programs underlying muscle maintenance and decline. Equally transformative are advances in epigenomic profiling, which have revealed how age-dependent changes in DNA methylation, histone modifications, chromatin accessibility, and non-coding RNA regulation profoundly influence muscle homeostasis. These modifications not only integrate environmental cues-such as nutrition, exercise, and metabolic state-but also mediate long-term transcriptional reprogramming, contributing to inter-individual variability in disease susceptibility and progression. In particular, the concept of the "epigenetic clock" has provided a powerful framework to link molecular aging signatures with muscle function decline, offering potential biomarkers for early detection and intervention [4, 7-9].

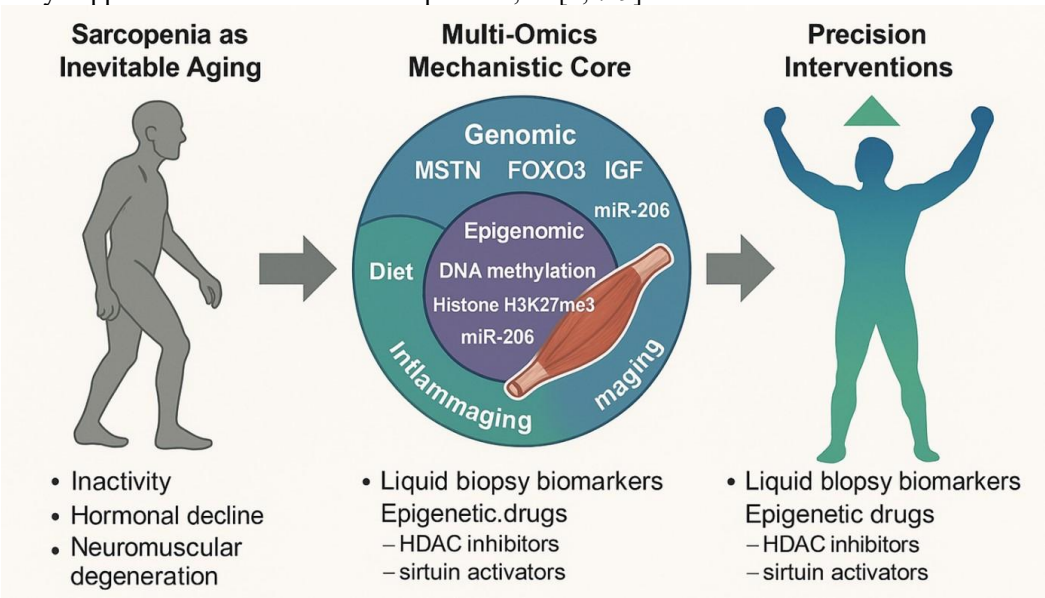

Figure 1. Genomic and Epigenomic Landscapes of Sarcopenia — From Aging to Precision Interventions. Sarcopenia evolves from an age-related degenerative condition to a molecularly regulated and potentially reversible syndrome. The left panel depicts aging-related muscle loss driven by inactivity and hormonal decline. The central panel illustrates the multi-omics core integrating genomic (*MSTN, FOXO3, IGF1*), epigenomic (DNA methylation, histone H3K27me3, miR-206), and environmental (diet, exercise, inflammaging) factors influencing muscle biology. The right panel highlights precision interventions, including liquid biopsy biomarkers, epigenetic drugs (HDAC inhibitors, sirtuin activators), and personalized lifestyle strategies.

Together, these genomic and epigenomic insights have catalyzed a paradigm shift-from viewing sarcopenia as a passive byproduct of aging to recognizing it as a molecularly regulated and potentially modifiable condition. This emerging perspective paves the way for precision medicine approaches that combine genetic risk profiling, epigenetic biomarkers, and targeted therapeutic interventions [10]. Ultimately, understanding the genomic and epigenomic landscapes of sarcopenia holds the key to developing predictive tools, preventive strategies, and personalized treatments aimed at preserving muscle health and extending healthspan in aging populations [11-12] (Fig. 1).

2. Genomic Determinants of Sarcopenia

2.1. Genetic Architecture and Heritability

Accumulating evidence from twin, family, and population-based studies indicates that genetic factors

account for approximately 40-60% of the inter-individual variability in skeletal muscle mass [13], strength, and functional decline. This substantial heritability underscores the biological importance of genetic predisposition in shaping muscle phenotypes throughout life [14]. Early linkage analyses and candidate-gene studies paved the way for more comprehensive genome-wide association studies (GWAS), which have now identified dozens of loci associated with key muscle-related traits, including muscle cross-sectional area, grip strength, fiber-type distribution, and susceptibility to sarcopenia [15].

Among the most well-characterized genetic contributors is MSTN (myostatin), a member of the TGF-β superfamily that functions as a potent negative regulator of muscle growth. Loss-of-function mutations in MSTN result in dramatic muscle hypertrophy, both in animal models and in rare human cases, highlighting the central role of myostatin signaling in muscle mass regulation. Similarly, ACTN3 [16-17], which encodes α-actinin-3, a structural protein in fast-twitch fibers, influences fiber-type composition and contractile capacity; the common R577X nonsense polymorphism has been associated with endurance vs. power phenotypes and age-related muscle decline [18-20].

Other key loci modulate anabolic signaling and muscle regeneration. Variants in IGF1 and AKT1 affect the IGF1–PI3K–AKT–mTOR pathway [21-22], a master regulator of muscle protein synthesis and hypertrophy [1]. PAX7 [24-26], a transcription factor critical for satellite cell specification and self-renewal, influences regenerative capacity and muscle plasticity during aging [27-29]. FOXO3, best known for its association with human longevity, modulates autophagy and proteostasis-processes that are indispensable for maintaining muscle quality over time [18, 22].

Beyond single-gene effects, polygenic models have revealed that sarcopenia is a highly polygenic and pleiotropic trait, influenced by a constellation of small-effect variants across the genome. Polygenic risk scores (PRS: A polygenic risk score is a quantitative measure of genetic susceptibility that aggregates the effects of multiple risk-associated variants across the genome) constructed from GWAS data can predict susceptibility to low muscle mass and poor physical performance, although predictive power varies across populations due to genetic diversity and gene-environment interactions. Notably, several loci implicated in muscle phenotypes also play roles in metabolic regulation, inflammatory signaling, and bone homeostasis, reflecting the interconnected nature of musculoskeletal aging.

2.2. Pathway-Level Insights

While GWAS have pinpointed numerous loci associated with sarcopenia, pathway-level analyses provide deeper mechanistic insight into how these genetic variants converge to influence muscle homeostasis. Several core biological processes emerge as central to the genomic architecture of sarcopenia:

2.2.1. Proteostasis and Autophagy

Maintenance of muscle mass requires a delicate balance between protein synthesis and degradation. Genes regulating the ubiquitin–proteasome system (UPS)-notably FBXO32 (Atrogin-1) and TRIM63 (MuRF1)-are consistently upregulated during muscle atrophy, promoting targeted degradation of contractile and structural proteins [30]. These E3 ubiquitin ligases are transcriptionally controlled by FOXO transcription factors, which integrate nutrient, hormonal, and stress signals. Dysregulation of UPS components leads to excessive proteolysis and muscle wasting, a hallmark of sarcopenia [31-32].

2.2.2. Mitochondrial Dynamics and Oxidative Stress

Mitochondrial quality control is another crucial determinant of muscle health. Genes involved in mitochondrial biogenesis, such as PPARGC1A (PGC-1α), coordinate oxidative metabolism and resistance to fatigue, while PINK1 and PRKN (Parkin) regulate mitophagy, the selective removal of damaged mitochondria [33]. Age-associated variants in these pathways impair mitochondrial turnover, leading to elevated reactive oxygen species (ROS), oxidative damage, and bioenergetic decline. Such defects not only compromise muscle endurance but also activate catabolic pathways that exacerbate atrophy [34].

2.2.3. Inflammation and Immune Signaling

Genetic polymorphisms in pro-inflammatory cytokines-including IL6, TNF, and IL1B -influence the chronic low-grade inflammatory state characteristic of aging ("inflammaging") [35-36]. Persistent activation of NF-κB and JAK–STAT signaling drives catabolic gene expression, impairs anabolic signaling, and reduces satellite cell function. This inflammatory milieu interacts with other genomic networks to accelerate muscle degeneration, highlighting the immunogenetic dimension of sarcopenia [37].

2.2.4. Regeneration and Stemness

Skeletal muscle possesses remarkable regenerative capacity, largely mediated by resident satellite cells.

However, aging disrupts this regenerative machinery [38]. Variants in MYOG (myogenin) and PAX7 modulate myogenic commitment and stem cell self-renewal, while NOTCH1 and WNT signaling components orchestrate the balance between quiescence, proliferation, and differentiation. Genetic perturbations in these pathways compromise regeneration, leading to reduced muscle fiber turnover and impaired repair following injury or stress [39].

2.2.5. Anabolic Signaling and Growth Regulation

The IGF1–PI3K–AKT–mTOR axis is a pivotal pathway promoting muscle protein synthesis, growth, and hypertrophy [40]. Variants that attenuate signaling through this cascade diminish anabolic capacity, contributing to sarcopenic phenotypes. Crosstalk with AMPK and SIRT1 pathways further integrates nutrient sensing and energy status into muscle growth regulation, illustrating the complex interplay between metabolic and genetic signals [22].

2.3. Integrated Polygenic Networks and Clinical Implications

The pathways described above do not operate in isolation; rather, they form a highly interconnected regulatory network that governs muscle mass and function. Variants within these networks often exhibit epistasis-non-additive interactions that modulate phenotypic outcomes-and are influenced by environmental modifiers such as physical activity, diet, hormonal status, and metabolic health. Epistasis describes non-additive interactions between genetic variants, whereby the effect of one gene depends on the presence of others. This complexity underscores why single-gene approaches have limited predictive value and why systems-level analyses are essential for understanding sarcopenia susceptibility [15, 41].

Clinically, integrating genomic information into predictive models could enable early identification of high-risk individuals and inform personalized interventions. For example, individuals carrying risk alleles in anabolic signaling pathways may benefit more from resistance training or protein supplementation, whereas those with variants affecting mitochondrial dynamics might respond better to interventions targeting oxidative metabolism. Ultimately, decoding the genetic architecture of sarcopenia provides not only mechanistic insights but also a foundation for precision geroscience-the tailoring of prevention and therapy to an individual's genetic and molecular profile [42-46].

2.3.1. Sex- and Ancestry-Specific Genetic Architecture of Sarcopenia

Sarcopenia exhibits marked sex-specific genetic and epigenetic heterogeneity, reflecting fundamental differences in hormonal regulation, muscle composition, and molecular aging trajectories between males and females. One of the best-characterized examples is the ACTN3 R577X polymorphism, which differentially affects fast-twitch fiber composition, muscle power, and age-related muscle decline in men and women. These genetic effects are further modulated by sex hormones, particularly testosterone, estrogen, and IGF-1, which regulate anabolic signaling, satellite cell activity, and epigenetic remodeling in skeletal muscle. Age-related declines in these hormones lead to sex-specific shifts in gene expression and DNA methylation patterns, contributing to divergent sarcopenia phenotypes between males and females.

In addition to sex differences, ancestry-dependent genetic architecture represents a major limitation in current sarcopenia genomics. Most genome-wide association studies and polygenic risk score models have been derived predominantly from populations of European ancestry, resulting in reduced predictive accuracy in Asian, African, and admixed populations. Differences in allele frequencies, linkage disequilibrium structure, and gene-environment interactions can substantially alter the effect sizes of sarcopenia-associated loci across populations, leading to biased risk estimation when European-derived models are applied globally.

These sex- and ancestry-specific effects underscore that sarcopenia is not a genetically uniform condition but a population- and context-dependent trait. Future precision geroscience approaches will therefore require ancestrally diverse cohorts and sex-aware genomic models to ensure accurate risk stratification, biomarker discovery, and personalized intervention strategies (Fig. 2).

3. Epigenomic Regulation of Muscle Aging

Epigenetic regulation [47], the reversible, heritable modification of gene expression without changes to the underlying DNA sequence-is a central mechanism linking environmental signals, metabolic state, and aging processes to the functional decline of skeletal muscle. Unlike static genetic variants, epigenetic marks are dynamic and plastic, integrating lifelong exposures such as diet, physical activity, hormonal fluctuations, inflammation, and oxidative stress. Age-associated epigenetic changes, collectively referred to as "epigenetic drift", profoundly reshape the transcriptional landscape of muscle cells, altering satellite cell function, metabolic capacity, regenerative potential, and stress responsiveness [48-54].

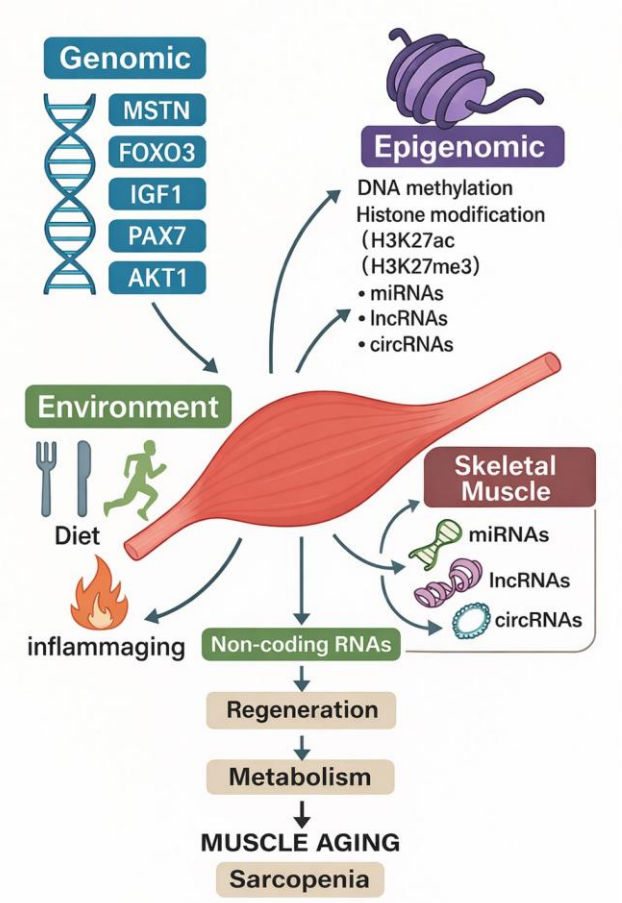

Figure 2. Epigenetic regulation of muscle aging in sarcopenia
This schematic illustrates how genomic, epigenomic, and environmental factors converge to regulate skeletal muscle regeneration and metabolism during aging. Genomic determinants (MSTN, FOXO3, IGF1, PAX7, AKT1) interact with epigenomic mechanisms, including DNA methylation, histone modifications (H3K27ac, H3K27me3), and non-coding RNAs (miRNAs, lncRNAs, circRNAs). Environmental influences such as diet, exercise, and inflammaging further reshape these regulatory networks. Together, these multilayered signals modulate myogenic gene expression and mitochondrial homeostasis, ultimately driving muscle aging and sarcopenia.

3.1. DNA Methylation and Epigenetic Drift

DNA methylation [55], the addition of a methyl group to cytosine residues (primarily at CpG dinucleotides), is one of the most studied epigenetic modifications in aging [56]. Skeletal muscle displays characteristic patterns of methylation change over time, including global hypomethylation, which contributes to genomic instability, and locus-specific hypermethylation, particularly at promoters and enhancers regulating key myogenic and metabolic genes. Such hypermethylation can repress the transcription of genes involved in satellite cell activation (PAX7, MYF5), myogenic differentiation (MYOD1, MYOG), and mitochondrial metabolism (PPARGC1A, CPT1B), thereby impairing regenerative capacity and metabolic flexibility [48-49, 57].Recent epigenome-wide association studies (EWAS) have identified thousands of age-associated differentially methylated regions (aDMRs) in skeletal muscle. These changes not only correlate with chronological age but also with biological age and functional parameters such as muscle strength, gait speed, and mitochondrial function. DNA methylation-based epigenetic clocks-including Horvath, Hannum, and GrimAge-show strong predictive power for sarcopenia risk and progression [56]. Importantly, accelerated epigenetic aging in muscle tissue has been linked to reduced satellite cell proliferation and impaired adaptive responses to exercise, suggesting a causal role in functional decline [51].

Moreover, DNA methylation patterns are highly sensitive to environmental and lifestyle factors [58]. Physical exercise, for example, induces rapid demethylation of enhancers associated with oxidative metabolism and mitochondrial biogenesis, while chronic inflammation can drive hypermethylation of anabolic signaling genes. Nutritional interventions (e.g., caloric restriction, NAD^+ supplementation) also remodel the muscle methylome, highlighting the dynamic and modifiable nature of this regulatory layer. Emerging single-cell methylome analyses further reveal cell type-specific epigenetic trajectories, distinguishing the epigenetic aging patterns of satellite cells, myonuclei, and fibro-adipogenic progenitors-a level of resolution that promises deeper mechanistic insight [51, 59].

3.2. Histone Modifications and Chromatin Remodeling

Histone modifications add a second layer of epigenetic complexity, modulating chromatin structure and accessibility to transcriptional machinery. Histone tails can undergo a range of post-translational modifications-including acetylation, methylation, phosphorylation, and ubiquitination-that collectively shape gene expression programs [60]. Aging muscle exhibits profound shifts in the histone modification landscape. H3K27ac, a marker of active enhancers, declines with age, reducing the transcription of genes involved in anabolic signaling (IGF1, AKT1) and mitochondrial biogenesis (PGC-1α) [61]. In contrast, H3K27me3, a repressive mark deposited by the polycomb repressive complex 2 (PRC2), becomes more abundant, silencing genes that regulate stem cell self-renewal and muscle regeneration. Similarly, increased H3K9me3, associated with heterochromatin formation, contributes to global chromatin condensation and transcriptional inflexibility. Chromatin accessibility

assays such as ATAC-seq have revealed that enhancers controlling myogenic transcription factors (e.g., MYOD1, MEF2C) and metabolic regulators (e.g., NRF1, ERRα) become progressively less accessible with age. This reduced plasticity compromises the muscle's ability to respond to physiological stimuli such as resistance exercise or nutrient availability. Moreover, altered interactions between histone modifiers-including histone acetyltransferases (HATs), histone deacetylases (HDACs), and histone methyltransferases (HMTs)-further distort transcriptional networks that maintain muscle mass and quality. Importantly, many of these histone changes are potentially reversible, offering therapeutic opportunities. HDAC inhibitors have shown promise in preclinical models by enhancing myogenic gene expression, improving satellite cell function, and attenuating muscle wasting. Similarly, small-molecule inhibitors targeting epigenetic enzymes such as EZH2 (a methyltransferase responsible for H3K27me3) are being explored for their potential to rejuvenate aged chromatin states and restore regenerative capacity [62-63].

3.3. Non-Coding RNAs and Post-Transcriptional Control

Beyond DNA and histone modifications, non-coding RNAs (ncRNAs) represent a crucial layer of epigenetic regulation in muscle aging. These include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), all of which fine-tune gene expression post-transcriptionally and influence chromatin states.

MicroRNAs, typically 20-24 nucleotides long, regulate gene expression by binding to complementary sequences in target mRNAs, leading to degradation or translational repression. Several muscle-enriched miRNAs-collectively known as myomiRs-are pivotal regulators of myogenesis and muscle maintenance. miR-1, miR-133a, and miR-206 promote myogenic differentiation, while miR-486 enhances PI3K–AKT signaling and suppresses FOXO-mediated atrophy pathways. Dysregulation of these miRNAs with age contributes to impaired satellite cell function and increased catabolism. Circulating miRNA profiles also hold potential as non-invasive biomarkers for sarcopenia diagnosis and prognosis [64].

LncRNAs (>200 nucleotides) exert regulatory control at multiple levels, from chromatin remodeling to mRNA stability [65]. H19, one of the best-characterized muscle lncRNAs, modulates IGF2 expression and promotes myogenic differentiation. Age-related downregulation of H19 impairs satellite cell activation, while aberrant expression of MALAT1 has been linked to defective regeneration and altered mitochondrial function [66]. Some lncRNAs act as scaffolds for chromatin-modifying complexes, influencing histone modifications and enhancer activity in muscle-specific gene loci [67-68].

Emerging evidence also implicates circRNAs-covalently closed RNA molecules with high stability-in muscle physiology and aging. Certain circRNAs act as "miRNA sponges," sequestering myomiRs and modulating their downstream effects. The precise roles of circRNAs in sarcopenia are still being elucidated, but their stability and tissue specificity make them attractive therapeutic and biomarker candidates [69-71].

Although circRNAs have emerged as important regulators of muscle regeneration and aging in murine models and cultured myoblasts, direct evidence for their functional roles in human sarcopenia remains limited. Most circRNA-myomiR and circRNA-chromatin interactions have been characterized in preclinical systems, and their relevance as clinical biomarkers or therapeutic targets in humans has yet to be established.

3.4. Integrative Epigenetic Networks and Therapeutic Potential

Epigenetic mechanisms do not act in isolation but form an interconnected regulatory network that dynamically links genomic potential with environmental context. DNA methylation can influence histone modification recruitment; ncRNAs can guide chromatin modifiers to specific loci; and histone states can shape the methylation landscape. This integrated network governs transcriptional plasticity, enabling skeletal muscle to adapt-or fail to adapt-to age-related stressors [72-73].

Crucially, the plastic and reversible nature of epigenetic marks positions them as promising therapeutic targets. Lifestyle interventions such as exercise, caloric restriction, and dietary modulation can partially reverse age-associated epigenetic changes, while pharmacological approaches targeting DNA methyltransferases, HDACs, or non-coding RNA pathways offer additional avenues for intervention. As our understanding deepens, combining these strategies with genomic risk profiling could enable precision epigenetic therapies aimed at preserving muscle mass and function well into old age [74-75].

3.5 Controversies, Variability, and Population-Specific Limitations in Sarcopenia Genomics and Epigenomics

Lifestyle and environmental factors, including physical activity, systemic inflammation, nutritional status, and metabolic health, represent major sources of biological variability in genomic, epigenomic, and transcriptomic biomarkers of sarcopenia. These extrinsic influences can

act as important confounders in cross-sectional biomarker studies, as molecular signatures may reflect not only intrinsic muscle aging but also recent or cumulative environmental exposures. Accordingly, careful adjustment for lifestyle and inflammatory status is essential for accurate interpretation and validation of multi-omics biomarkers in sarcopenia research.

Despite rapid progress in sarcopenia genomics and epigenomics, substantial heterogeneity and unresolved controversies remain. One of the most prominent challenges is the variable performance of epigenetic clocks in predicting muscle aging and sarcopenia. While DNA methylation–based clocks such as Horvath, GrimAge, and muscle-specific clocks correlate with chronological age, their ability to predict muscle mass, strength, and physical performance differs across tissues, cohorts, and study designs. Blood-based clocks often show weaker associations with muscle phenotypes than muscle-derived methylation profiles, underscoring the tissue-specific nature of epigenetic aging.

Similarly, the clinical utility of polygenic risk scores (PRS) for sarcopenia remains limited by population heterogeneity. Most GWAS underlying current PRS models are heavily biased toward individuals of European ancestry, reducing their transferability to Asian, African, and admixed populations. Differences in allele frequencies, linkage disequilibrium structure, and gene–environment interactions can lead to inaccurate risk estimation and reduced predictive power outside the discovery populations.

Another source of inconsistency arises from differences in sarcopenia definitions and phenotyping across studies. Diagnostic criteria based on muscle mass, grip strength, gait speed, or composite frailty indices capture overlapping but non-identical biological states, leading to variable genomic and epigenomic associations. This heterogeneity complicates meta-analyses and limits direct comparison between cohorts.

Epigenetic biomarkers are also influenced by environmental and lifestyle factors such as physical activity, inflammation, and nutrition, which vary widely between populations and across the life course. As a result, epigenetic age acceleration and methylation-based risk signatures may reflect both intrinsic biological aging and extrinsic exposures, introducing additional variability into EWAS findings.

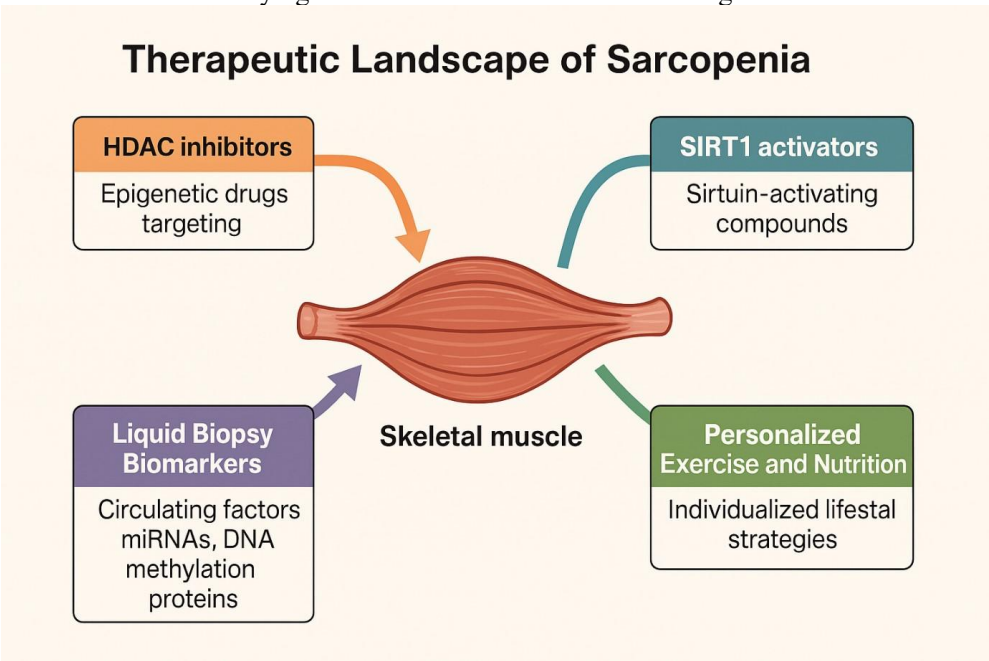

Figure 3. Therapeutic landscape and precision interventions for sarcopenia. This diagram summarizes emerging precision strategies targeting the molecular mechanisms of sarcopenia. Epigenetic modulators such as HDAC inhibitors restore anabolic gene expression, while SIRT1 activators enhance mitochondrial function and oxidative metabolism. Liquid biopsy biomarkers-including circulating miRNAs, methylated DNA fragments, and muscle-derived proteins-enable early detection and monitoring of disease progression. Personalized exercise and nutrition programs complement these pharmacological approaches by promoting epigenetic remodeling and metabolic rejuvenation. Together, these interventions represent an integrated therapeutic framework linking molecular insights to individualized prevention and treatment of muscle aging.

Together, these limitations highlight that neither epigenetic clocks nor PRS should currently be interpreted as universal or deterministic predictors of sarcopenia. Instead, their value lies in probabilistic risk stratification

within specific populations and clinical contexts. Addressing these challenges will require larger, ancestrally diverse cohorts, standardized phenotyping, and integrative multi-omics approaches that explicitly model gene-environment interactions (Fig. 3).

4. Gene-Environment Interactions and Systemic Influences

While genetic architecture establishes the baseline risk for sarcopenia, it is increasingly evident that environmental factors shape how this risk is manifested. Epigenetic regulation serves as the critical molecular interface connecting the genome to external stimuli, translating environmental inputs into gene expression programs that govern muscle plasticity, metabolic state, and regenerative capacity. This interplay between genes and environment explains why individuals with similar genetic backgrounds can exhibit vastly different trajectories of muscle aging-and why interventions targeting lifestyle and systemic factors can profoundly influence outcomes.

4.1. Exercise-Induced Epigenetic Remodeling

Physical activity is one of the most potent modulators of the muscle epigenome. Both endurance and resistance exercise trigger widespread epigenetic remodeling, including DNA demethylation, enhancer activation, and chromatin accessibility changes in genes associated with mitochondrial biogenesis, oxidative metabolism, and muscle hypertrophy. For instance, acute exercise rapidly demethylates regulatory regions of *PPARGC1A* (*PGC-1α*), *NRF1*, and *TFAM*, thereby enhancing mitochondrial transcription and energy production. Chronic training leads to persistent epigenetic reprogramming, establishing "molecular memory" that primes muscle for future adaptation-a phenomenon referred to as epigenetic muscle memory [60, 76].

Exercise also modulates histone acetylation through the activity of metabolic sensors such as *AMPK* and *SIRT1*, which link cellular energy status to chromatin state. Increased H3K27ac at promoters of anabolic and oxidative genes enhances transcriptional activation, while decreased repressive marks (e.g., H3K27me3) promote myogenic differentiation. These changes extend beyond muscle cells: exercise-induced circulating miRNAs and myokines can modulate gene expression in distant tissues, highlighting the systemic nature of epigenetic reprogramming [55, 77-78].

4.2. Nutritional Modulation of the Epigenome

Nutritional status exerts profound influence on the epigenetic regulation of muscle function. Caloric restriction-one of the most robust interventions to extend lifespan and healthspan-alters DNA methylation dynamics and enhances the expression of genes involved in autophagy, mitochondrial turnover, and oxidative phosphorylation. Nutrient availability modulates the activity of key epigenetic enzymes: S-adenosylmethionine (SAM) serves as a methyl donor for DNA and histone methylation, while acetyl-CoA availability influences histone acetylation levels [79-82].

Amino acid supplementation, particularly leucine and branched-chain amino acids (BCAAs), activates mTORC1 signaling and influences the epigenetic landscape of anabolic genes. Similarly, dietary polyphenols (e.g., resveratrol) and NAD^+ boosters (e.g., nicotinamide riboside) activate sirtuins, histone deacetylases that enhance mitochondrial function and oxidative metabolism. These diet–epigenome interactions suggest that nutritional interventions can "recalibrate" gene expression programs and delay or reverse aspects of muscle aging [83-84].

4.3. Hormonal Regulation and Systemic Endocrine Influences

Hormonal milieu-particularly anabolic hormones such as testosterone, growth hormone (GH), and insulin-like growth factor 1 (IGF-1)-profoundly impacts muscle mass and function, in part through epigenetic mechanisms [85]. Age-related declines in these hormones are associated with increased DNA methylation of anabolic pathway genes and reduced chromatin accessibility at promoters of growth-regulating factors. Hormone replacement or modulation can reverse some of these epigenetic alterations, restoring anabolic signaling and improving muscle regenerative capacity [86].

Furthermore, glucocorticoids and thyroid hormones influence chromatin states and transcriptional networks involved in catabolism, mitochondrial turnover, and metabolic regulation. Dysregulation of these pathways-such as chronic hypercortisolemia-leads to persistent activation of muscle atrophy genes (e.g., FOXO1, Atrogin-1) and reinforces catabolic epigenetic states, contributing to sarcopenia progression [85-87].

4.4. Inflammation, Immunometabolism, and Epigenetic Crosstalk

Chronic low-grade inflammation ("inflammaging") represents another key environmental driver of sarcopenia. Persistent elevation of cytokines such as IL-6, TNF-α, and IL-1β activates NF-κB and JAK–STAT pathways, inducing catabolic gene expression and altering

the epigenetic landscape of muscle tissue. Inflammatory signaling can promote hypermethylation of myogenic promoters, reduce histone acetylation, and disrupt enhancer activity, thereby suppressing regenerative programs [88-90].

At the same time, metabolic-immune crosstalk further shapes these epigenetic responses. For example, elevated ROS and metabolic byproducts influence DNA methyltransferase (DNMT) and histone deacetylase (HDAC) activity, reinforcing a pro-inflammatory and catabolic chromatin state. Conversely, interventions that reduce systemic inflammation-including anti-inflammatory diets, regular physical activity, and senolytic therapies-can attenuate these deleterious epigenetic changes and restore anabolic signaling [91].

4.5. Environmental Exposures, Aging Milieu, and Transgenerational Effects

Beyond lifestyle, environmental exposures such as pollutants, endocrine disruptors, and xenobiotics can modulate the muscle epigenome [92]. Chronic exposure to heavy metals or endocrine-disrupting chemicals has been linked to aberrant methylation patterns and impaired mitochondrial gene regulation [93-94]. Moreover, recent studies suggest that early-life exposures-including prenatal nutrition and maternal inflammation-can induce transgenerational epigenetic modifications that influence muscle development and sarcopenia risk decades later [95-96].

The aging systemic environment itself-characterized by altered cytokine levels, extracellular vesicle signaling, and circulating metabolites-also plays a pivotal role. Parabiosis experiments in mice have shown that exposure of aged muscle to a young systemic milieu can rejuvenate epigenetic states and restore regenerative potential, underscoring the systemic regulation of muscle aging [97-99].

4.6. Therapeutic and Predictive Implications

The plastic and reversible nature of epigenetic marks makes them attractive targets for precision interventions [100]. Combining genomic risk profiling with epigenetic biomarkers could enable the development of personalized prevention strategies-tailoring exercise regimens, dietary interventions, and pharmacological treatments to an individual's molecular profile. Furthermore, longitudinal monitoring of epigenetic signatures may allow early detection of sarcopenia risk and dynamic assessment of intervention efficacy [72, 101].

Ultimately, understanding how environmental and systemic factors sculpt the muscle epigenome offers a powerful framework for shifting from reactive to preventive and precision geroscience. Rather than treating sarcopenia as an inevitable consequence of aging, these insights open the door to targeted strategies that harness gene-environment interplay to preserve muscle function and extend healthspan [51, 102-103].

5. Toward Precision Diagnostics and Therapies

The rapid accumulation of multi-omics data and the growing understanding of genomic-epigenomic interplay are transforming how sarcopenia is diagnosed, stratified, and treated. Once considered an irreversible feature of aging, sarcopenia is now increasingly viewed as a modifiable condition, with intervention opportunities emerging across the continuum-from early detection to disease modification and functional restoration. The integration of high-resolution molecular profiling with clinical decision-making represents a paradigm shift toward precision geroscience [104].

5.1. Multi-Omics Biomarker Discovery

To bridge the traditionally siloed GWAS, EWAS, and transcriptomic findings, we introduce an integrated multi-omics framework in which genetic variants define baseline susceptibility, epigenetic modifications encode environmental and aging-related exposures, and transcriptomic programs reflect real-time functional states of skeletal muscle. Within this framework, sarcopenia emerges as a systems-level phenotype driven by the dynamic interaction of these molecular layers, converging on key biological axes including anabolic signaling, mitochondrial homeostasis, and chronic inflammation. This integrative model provides a mechanistic basis for interpreting heterogeneous biomarker signatures and enables more accurate prediction of disease trajectories and therapeutic responses.

The complexity and heterogeneity of sarcopenia necessitate multi-layered biomarkers that capture genetic risk, epigenetic state, transcriptional dynamics, and proteomic signatures. Traditional clinical markers-such as grip strength, walking speed, or muscle cross-sectional area-lack sensitivity for early detection and do not reflect underlying molecular changes. In contrast, multi-omics approaches provide a comprehensive molecular fingerprint of sarcopenia onset and trajectory [105-106]. Genomic biomarkers-including risk alleles in *MSTN*, *FOXO3*, *IGF1*, and *PAX7*-inform baseline susceptibility, while epigenomic signatures (e.g., DNA methylation age acceleration, histone modification patterns, or circulating miRNA profiles) capture dynamic disease activity. Transcriptomic markers, derived from bulk and single-cell RNA sequencing, can identify dysregulated pathways such as autophagy, mitochondrial biogenesis, and

immune signaling, whereas proteomic and metabolomic profiles offer real-time snapshots of anabolic/catabolic balance and metabolic health [107].

Integrative computational frameworks such as multi-omics network analysis, machine learning classifiers, and Bayesian data fusion are increasingly used to combine these layers into predictive models that provide a comprehensive understanding of the molecular mechanisms underlying muscle aging and sarcopenia. These approaches enable the identification of key regulatory nodes, reveal causal relationships among epigenetic, transcriptomic, and metabolic pathways, and offer systems-level insights into how molecular alterations collectively drive the decline in muscle mass and function. Circulating biomarkers, including plasma miRNAs (e.g., miR-206, miR-486), cell-free methylated DNA fragments, and muscle-derived extracellular vesicles, are emerging as non-invasive liquid biopsy tools, offering new avenues for early detection and longitudinal monitoring [108-109].

5.1.1. Methodological Limitations and Interpretative Caution

Despite the transformative potential of EWAS, single-cell sequencing, and epigenome-editing technologies in sarcopenia research, each of these approaches carries important technical and conceptual limitations. In older adults, blood-based genomic and epigenomic biomarkers can be influenced by clonal hematopoiesis of indeterminate potential (CHIP), an age-related expansion of hematopoietic cell clones that alters mutation profiles and DNA methylation patterns in peripheral blood. Consequently, blood-derived molecular signatures may not reliably represent skeletal muscle-specific aging or sarcopenia-related processes, and should therefore be interpreted with caution and, whenever feasible, corroborated with muscle tissue–based molecular or functional assessments.

EWAS are particularly sensitive to batch effects, tissue heterogeneity, and differences in sample processing, which can generate spurious associations if not rigorously controlled. Moreover, blood-derived methylation profiles often do not accurately reflect muscle-specific epigenetic states, complicating biological interpretation.

Single-cell transcriptomic and epigenomic analyses offer unprecedented resolution but remain vulnerable to technical noise, dropout effects, and challenges in accurately defining cell identities within heterogeneous muscle tissue. Rare but functionally important populations, such as satellite cells, can be underrepresented or misclassified, potentially biasing conclusions about regenerative capacity and aging trajectories.

Epigenome-editing approaches, including CRISPR/dCas9-based modulation of DNA methylation and histone marks, provide powerful tools for causal inference and therapeutic development. However, off-target effects, incomplete editing, and long-term stability of epigenetic modifications remain significant concerns. In addition, ethical and regulatory issues surrounding germline or long-lasting epigenetic modification must be carefully considered before clinical translation.

Together, these limitations highlight the need for cautious interpretation of multi-omics data and epigenetic interventions in sarcopenia, emphasizing the importance of replication, cross-platform validation, and rigorous methodological control.

5.2. Therapeutic Targeting of Epigenetic Modulators

The reversibility of epigenetic modifications makes them highly attractive therapeutic targets. A growing number of small-molecule agents are being developed to manipulate epigenetic regulators and restore youthful transcriptional states in aged muscle. Histone deacetylase (HDAC) inhibitors such as valproic acid or vorinostat enhance acetylation at promoters of anabolic and regenerative genes, improving satellite cell function and muscle mass [73, 110-111].

DNA methyltransferase (DNMT) inhibitors such as decitabine and azacitidine can reverse hypermethylation-associated gene silencing, thereby restoring the expression of key myogenic transcription factors.

In parallel, sirtuin activators including resveratrol and NAD^+ precursors promote mitochondrial biogenesis and enhance oxidative capacity by regulating histone deacetylation and chromatin remodeling. Beyond small-molecule approaches, RNA-based therapeutics are also gaining significant momentum. miRNA mimics-such as miR-206 replacement-can reactivate impaired myogenic programs, while anti-miRs targeting catabolic miRNAs help suppress atrophy pathways. Likewise, modulators of lncRNAs or mimetics of circRNAs can reshape chromatin topology and fine-tune transcriptional output, offering new layers of epigenetic control for muscle regeneration. Cutting-edge strategies also include epigenome editing using CRISPR/dCas9-based systems fused to epigenetic modifiers (e.g., TET demethylases, HATs, or KRAB repressors) [112]. These tools enable locus-specific reprogramming of DNA methylation or histone marks, offering unprecedented precision in restoring normal gene expression without altering the genome sequence.

An emerging concept is epigenetic rejuvenation therapy, which aims to reset aged chromatin states toward a more youthful configuration. Partial reprogramming,

which involves the transient activation of Yamanaka factors (OSKM: OCT4, SOX2, KLF4, and c-MYC) to restore youthful epigenetic states without inducing full cellular dedifferentiation, has shown promising effects in animal models, improving muscle regeneration and function without triggering pluripotency [113].

Partial epigenetic reprogramming using Yamanaka factors (OSKM) has shown promising effects on muscle regeneration and aging phenotypes in animal models; however, these approaches remain at a preclinical stage. Their safety, durability, and potential oncogenic risks in humans are largely unknown, and no controlled clinical studies have yet validated their applicability to human sarcopenia.

5.3. Personalized Intervention Strategies

The future of sarcopenia management lies in personalized, data-driven interventions that integrate genomic risk profiling, epigenetic state assessment, and lifestyle modulation. By combining these molecular insights with clinical phenotyping, it will be possible to tailor prevention and treatment strategies to an individual's unique biology [114-115].

Precision lifestyle interventions represent the first frontier. Individuals with high genetic risk but a relatively plastic epigenome may benefit most from targeted exercise regimens (e.g., resistance training for anabolic pathway activation) and specific nutritional interventions (e.g., leucine supplementation or NAD^+ boosters) [116]. Conversely, those with heavily methylated myogenic loci may require pharmacological demethylating agents or HDAC inhibitors to "unlock" regenerative potential before lifestyle interventions can exert maximal effect. In the therapeutic realm, multi-omics-guided decision support systems could recommend targeted combinations of pharmacological agents, RNA therapeutics, and lifestyle modifications. For example, patients carrying PINK1 or PRKN variants accompanied by mitochondrial dysfunction could benefit from a combination of sirtuin activators and aerobic training. Individuals showing elevated inflammatory cytokine signaling may be guided toward anti-inflammatory therapies combined with exercise-induced epigenetic remodeling. Those exhibiting accelerated epigenetic aging could be considered for DNMT inhibition or transient reprogramming approaches to restore youthful molecular profiles.

Moreover, longitudinal tracking of epigenetic biomarkers could inform adaptive therapy paradigms, where interventions are dynamically adjusted in response to molecular readouts -akin to precision oncology approaches. Such strategies promise not only to slow disease progression but also to restore muscle function and resilience (Fig. 4).

5.4. Future Perspectives: Toward Preventive Geroscience

The integration of genomic and epigenomic insights into clinical practice marks a transformative step toward preventive geroscience-a field aimed at extending healthspan by targeting the fundamental biological mechanisms of aging. In the case of sarcopenia, this means moving beyond symptomatic management toward early detection, molecular risk stratification, and targeted, mechanism-based interventions [117].

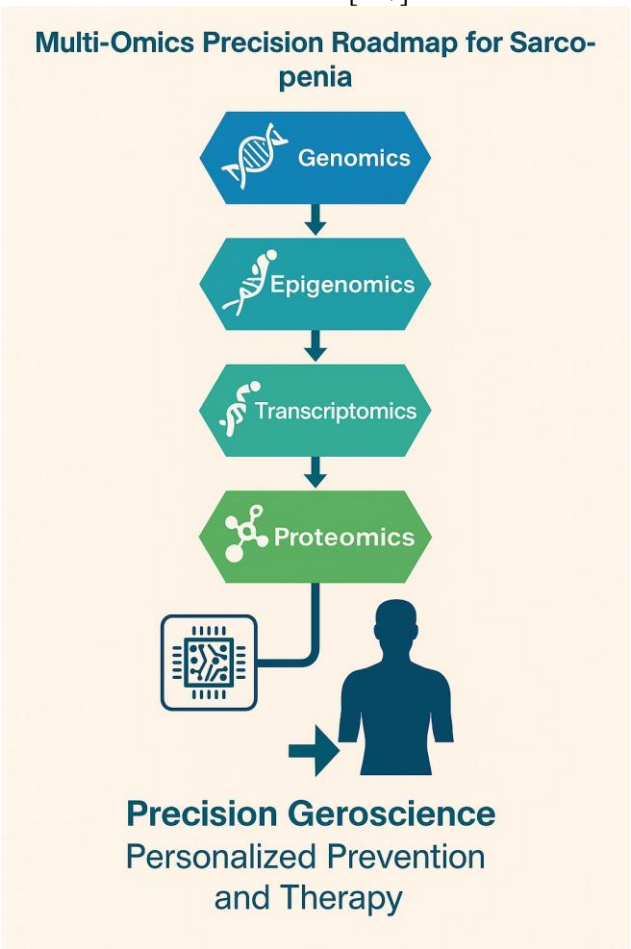

Figure 4. Integration of multi-omics layers for precision geroscience. Genomic, epigenomic, transcriptomic, and proteomic data are sequentially integrated through computational pipelines to generate individualized molecular profiles. These multi-layered insights enable precision geroscience, guiding personalized prevention and therapeutic strategies aimed at maintaining muscle health and extending healthspan.

Ultimately, precision diagnostics and therapies rooted in multi-omics data hold the promise of converting sarcopenia from an inevitable feature of aging into a manageable, and potentially reversible, condition. As the next decade unfolds, combining systems-level molecular profiling, AI-driven predictive modeling, and

interventional epigenetics will pave the way for truly personalized strategies to preserve muscle health and extend functional longevity [118-121].

6. Conclusions and Future Directions

The convergence of genomics, epigenomics, and systems biology is fundamentally transforming our understanding of sarcopenia, redefining it from a descriptive age-associated condition into a molecularly defined, mechanistically tractable syndrome. Genetic predispositions establish the foundational landscape of susceptibility, but it is the dynamic epigenetic regulation-shaped by environment, lifestyle, and systemic context-that ultimately determines whether, when, and how sarcopenia manifests. This interplay underscores a central principle of modern geroscience: aging is not solely a passive process but a biologically modifiable trajectory.

The integration of multi-omics technologies has illuminated this complexity with unprecedented resolution. Large-scale genome-wide association studies (GWAS) continue to expand the catalog of genetic loci associated with muscle phenotypes, while epigenome-wide association studies (EWAS) and single-cell multi-omics approaches are revealing how cell-type-specific regulatory landscapes evolve during aging. Spatial transcriptomics and multi-modal profiling promise to map the molecular heterogeneity of muscle tissue in situ, capturing the interplay between myonuclei, satellite cells, immune cells, and stromal components. Together, these approaches will allow researchers to move beyond static snapshots toward a dynamic, systems-level model of muscle aging [119].

Looking forward, several key research priorities stand out.

First, longitudinal cohort studies integrating genomic, epigenomic, transcriptomic, proteomic, and metabolomic data will be essential to understand the temporal sequence of molecular events leading to sarcopenia and to identify predictive biomarkers long before clinical onset.

Second, functional validation of candidate genes and regulatory networks-using advanced in vitro models (e.g., organoids, engineered muscle tissues) and in vivo gene-editing technologies-will be crucial to establish causal relationships and therapeutic targets.

Third, machine learning and artificial intelligence will play an increasingly central role in integrating complex multi-omics datasets, enabling predictive modeling of disease trajectories, response to interventions, and identification of novel therapeutic entry points.

At the translational level, the growing knowledge of the genomic and epigenomic underpinnings of sarcopenia offers a pathway toward precision geriatric medicine. By combining genomic risk profiling with real-time epigenetic monitoring, clinicians could soon stratify patients based on molecular risk, tailor preventive interventions, and dynamically adjust therapies in response to epigenetic feedback. Pharmacological targeting of epigenetic enzymes, RNA-based therapeutics, and locus-specific epigenome editing hold the promise of reversing maladaptive molecular programs, while lifestyle interventions such as exercise and nutrition can be precisely optimized to exploit epigenetic plasticity. Moreover, these advances have profound implications beyond sarcopenia itself. Because muscle health is intricately linked to metabolic regulation, immune competence, and systemic resilience, strategies that preserve skeletal muscle may also mitigate broader age-related conditions-from frailty and osteoporosis to type 2 diabetes and neurodegeneration. Thus, combating sarcopenia is not merely about maintaining muscle mass; it is a gateway to extending healthspan and functional independence in aging populations [122-123].

In conclusion, decoding the genomic and epigenomic landscapes of sarcopenia marks the beginning of a new era in aging research-one where molecular signatures guide clinical decision-making, interventions are tailored to individual biology, and aging itself becomes a modifiable process. As the field advances, interdisciplinary collaboration between molecular biologists, geriatricians, bioinformaticians, and public health experts will be essential to translate these discoveries into clinical practice. The ultimate goal is clear: to transform sarcopenia from an inevitable consequence of aging into a preventable, diagnosable, and treatable condition, thereby paving the way for healthier, longer, and more resilient lives.

Future progress in sarcopenia research will depend on the adoption of integrative and forward-looking methodological frameworks that move beyond cross-sectional and population-restricted studies. Large-scale cohorts that are ancestrally and sex diverse will be essential to ensure that genetic and epigenetic risk models are broadly generalizable and clinically applicable across different populations. In parallel, longitudinal multi-omics profiling-including genomics, epigenomics, transcriptomics, proteomics, and metabolomics-will be required to resolve the temporal sequence of molecular events that precede and drive muscle loss, rather than merely capturing static snapshots of advanced disease.

Equally important is the prioritization of tissue-specific analyses. Because blood-based biomarkers are influenced by hematopoietic dynamics, inflammation, and clonal expansion with aging, direct profiling of

skeletal muscle tissue and its resident cell populations will be critical for accurately defining disease-relevant molecular mechanisms. The integration of muscle-derived molecular data with circulating biomarkers will allow the development of more robust and clinically translatable diagnostic and prognostic tools.

Finally, advanced computational approaches-including network-based modeling, causal inference, and machine learning-will be indispensable for integrating these high-dimensional datasets into predictive frameworks. Such systems-level strategies will enable individualized risk stratification, identification of actionable molecular targets, and rational design of personalized interventions, thereby accelerating the transition of sarcopenia research from descriptive gerontology to precision geroscience.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conceptualization, J.Y.S.; methodology, J.Y.S.; formal analysis, J.Y.S.; writing – original draft, J.Y.S.; writing – review and editing, J.Y.S, J.W.L.; supervision, J.Y.S.; funding acquisition, J.W.L.; Both authors have read and agreed to the published version of the manuscript.

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