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Muscle: A Pivotal Player in Systemic Disease, a call for Clinical Research

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Abstract

Metabolic and neurodegenerative conditions pose a significant global health challenge, necessitating innovative strategies that address underlying mechanisms rather than merely managing symptoms. Emerging research highlights skeletal muscle as a central regulator of systemic metabolism and inter-organ communication, mediated by its secretome, epigenetic plasticity, and structural integrity. The muscle secretome, a complex array of signaling proteins, influences lipid and glucose metabolism, tissue remodeling, and neuroprotective pathways, thereby offering new avenues for biomarker discovery and therapeutic intervention. Epigenetic regulation—encompassing DNA methylation, histone modifications, and miRNA expression—mediates exercise-induced transcriptional adaptations that enhance mitochondrial biogenesis, metabolic flexibility, and inflammatory control. Conversely, muscle atrophy disrupts these adaptive processes, contributing to insulin resistance, chronic inflammation, and neurodegeneration through altered proteostasis and mitochondrial dysfunction. These interconnected mechanisms underscore skeletal muscle's pivotal role in maintaining systemic homeostasis. Interventions such as exercise training, nutritional modulation, and pharmacological targeting of myokines or epigenetic enzymes show promise for personalized therapies. Future research should prioritize integrative approaches that examine the crosstalk between muscle-derived factors, metabolic regulation, and neuroplasticity. Understanding how the muscle secretome and its epigenetic regulation interact to prevent atrophy and promote resilience could transform the management of metabolic and neurodegenerative disorders, paving the way for precision medicine.

Keywords: Muscle secretome; Epigenetic regulation; Muscle atrophy; Metabolic and neurodegenerative diseases; Personalized interventions

The increasing prevalence of metabolic and neurodegenerative diseases represents a significant global health challenge [1,2]. Current treatments for metabolic and neurodegenerative diseases focus on symptom management, but new therapies targeting underlying causes are urgently needed. Research highlights the importance of genetics, the gut microbiome, skeletal muscle, and exercise in metabolic and neurological regulation. Single-cell transcriptomics helps identify key pathways, while gut microbiome modulation offers a promising therapeutic approach. Exercise and muscle health improve insulin sensitivity and reduce inflammation, potentially altering disease progression. These research areas hold great promise for developing novel treatments that go beyond symptom relief [2-5]. Skeletal muscle, traditionally viewed primarily for its role in locomotion, has emerged as a promising therapeutic target due to its multifaceted systemic influence. This influence is exerted through the muscle secretome, a complex array of signaling molecules, and is modulated by epigenetic modifications and impacted by muscle atrophy. This editorial advocates for increased clinical research focusing on muscle as a central player in the development and progression of these diseases[6,7]. High-resolution proteomic analysis of muscle secretome activity has revealed differentially expressed proteins in response to stimuli such as exercise, myogenesis, and metabolic stress. For instance, the release of myokines like IL-6 during muscle contraction directly influences lipid and glucose metabolism regulation, while proteins like myostatin inhibit muscle hypertrophy, underscoring their impact on tissue dynamics. The specific regulation of these proteins under pathophysiological conditions, such as insulin resistance or dystrophin deficiency, highlights their potential as biomarkers and therapeutic targets. Studies have identified over 650 proteins within the muscle secretome, a subset of which exhibits differential regulation in response to factors like atrophy and insulin stimulation, opening avenues for personalized interventions (Fig. 1). Modulating the composition and activity of the secretome holds significant therapeutic potential[8,9].

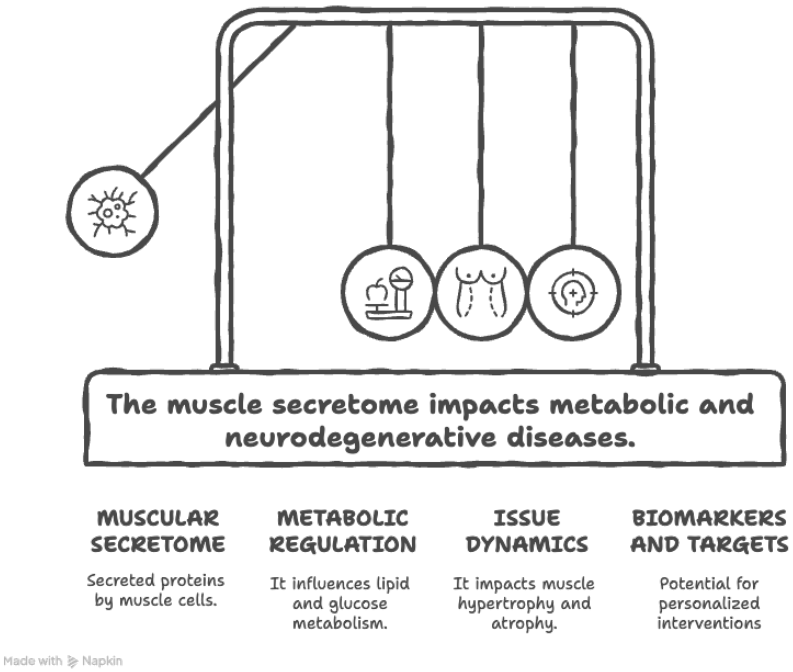

Figura 1: Conceptual model of the muscle secretome and its systemic impact.. The figure illustrates how the muscle secretome—comprising proteins secreted by skeletal muscle cells—acts as a key regulator of inter-organ communication. Through its secreted factors, skeletal muscle modulates metabolic regulation, influencing lipid and glucose metabolism, and contributes to tissue dynamics, affecting structural and functional homeostasis. These mechanisms have direct implications for metabolic and neurodegenerative diseases, highlighting the muscle secretome as a potential source of biomarkers and therapeutic targets. Ultimately, understanding these pathways opens opportunities for personalized interventions within the framework of precision medicine.

Epigenetics, heritable changes in gene expression without alterations to DNA sequence, plays a crucial role in regulating skeletal muscle function and adaptability. Exercise induces significant epigenetic modifications, including DNA hypomethylation and histone modifications, impacting the transcription of genes involved in protein synthesis, myokine production, and energy metabolism. Specifically, exercise-induced hypomethylation of key genes like PGC-1, a regulator of mitochondrial biogenesis, fatty acid transport, and insulin sensitivity, facilitates complex metabolic adaptations essential for muscle performance and energy homeostasis. These modifications enable the muscle to adjust gene expression in response to stimuli like energy expenditure and oxidative stress, promoting metabolic flexibility and responsiveness to physiological demands[10,11]. Furthermore, exercise influences histone modification patterns, such as H3K27 acetylation and H3 phosphorylation, which relax chromatin and permit active transcription of genes related to muscle adaptation. These modifications can persist long after exercise cessation, creating a "metabolic memory"within the muscle that optimizes responses to future stimuli. This process also involves miRNA regulation and emerging epigenetic mechanisms like lysine lactylation, facilitating intercellular

communication between muscle and distant tissues. Collectively, these epigenetic modifications form a complex regulatory system that enables muscle to maintain adaptive structural and functional plasticity, crucial for preventing and treating metabolic diseases and enhancing performance in physically active individuals(Fig. 2)[12,13].

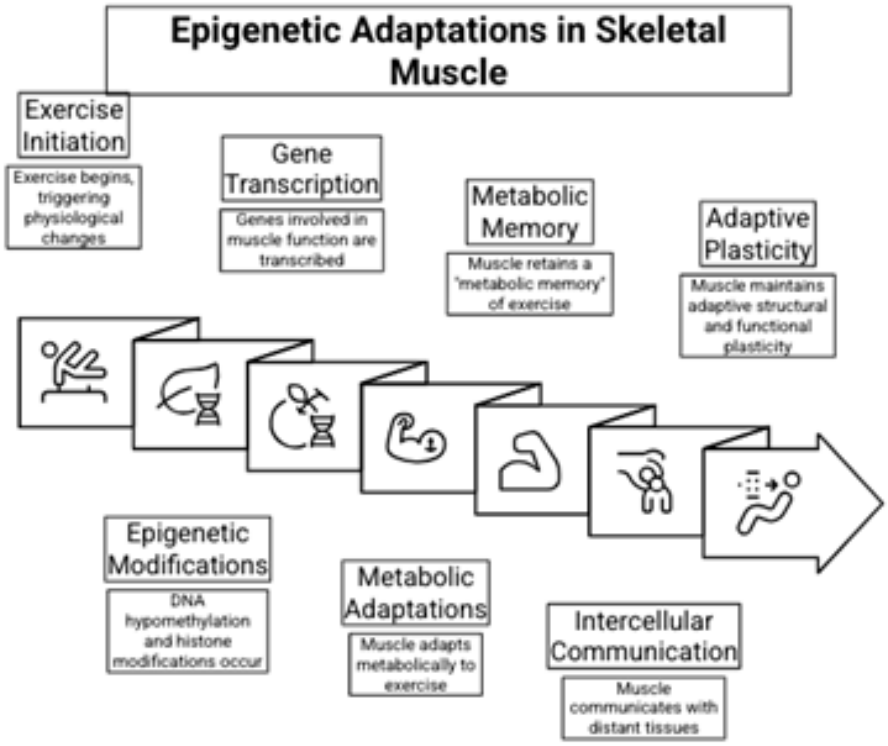

Figura 2: Epigenetic adaptations in skeletal muscle induced by exercise. Schematic representation of the sequential mechanisms by which exercise triggers epigenetic changes in skeletal muscle. Exercise initiation activates signaling pathways that promote gene transcription of metabolic and structural regulators. DNA hypomethylation and histone modifications (acetylation, phosphorylation) facilitate chromatin relaxation and expression of genes such as PGC-1, enhancing mitochondrial biogenesis, fatty acid transport, and insulin sensitivity. These processes drive metabolic adaptations and establish a "metabolic memory", enabling faster responses to future exercise. Intercellular communication via myokines and microRNAs supports systemic regulation, sustaining adaptive structural and functional plasticity of trained muscle.

Muscle atrophy, defined by a reduction in muscle mass and strength, is a prevalent comorbidity in numerous metabolic and neurodegenerative disorders, posing a significant challenge to health and well-being. This decline in muscle mass not only impairs mobility but also contributes to disease progression, notably in type 2 diabetes, where it exacerbates insulin resistance and promotes chronic inflammation[14]. The underlying mechanisms involve an imbalance in protein synthesis and degradation pathways, particularly the activation of atrogenes such as FoxO and NF-B, which stimulate proteolysis via the ubiquitin-proteasome system[15,16]. Furthermore, lipid accumulation and mitochondrial dysfunction within muscle fibers, especially in the context of a high-fat diet, worsen inflammation and insulin resistance, contributing

to muscle loss. These processes are amplified in chronic disease states and with "Western"dietary patterns, underscoring the need for therapeutic interventions that not only prevent muscle loss but also promote its recovery by targeting the signaling pathways and inflammatory milieu underlying this pathology(Fig.3) [17,18].

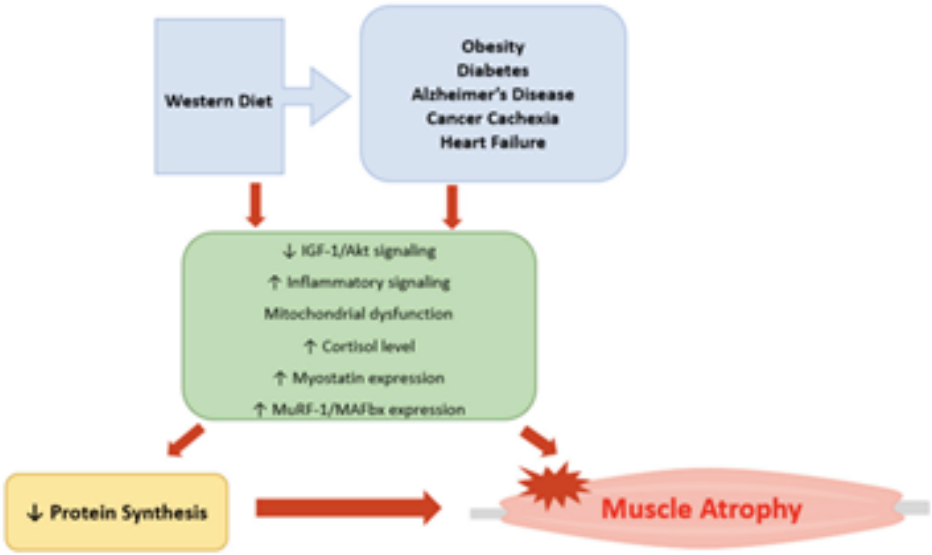

Figura 3: Skeletal muscle atrophy results from an imbalance between protein synthesis and degradation. Conditions like a Western diet, obesity, diabetes, Alzheimer's, cancer cachexia, and heart failure inhibit IGF-1/Akt signaling, increase inflammatory signaling and myostatin expression, and upregulate atrogenes (MuRF-1 and MAFbx), leading to reduced protein synthesis and increased degradation. Mitochondrial dysfunction also plays a role.

These three factors—secretome, epigenetics, and atrophy—are interconnected and play a synergistic role in systemic disease. Exercise, a potent stimulus for muscle adaptation, can positively influence all three. It can promote the release of beneficial myokines, induce favorable epigenetic modifications, and prevent muscle atrophy. A holistic approach that considers all three aspects is essential for developing effective therapeutic strategies.For example, a clinical trial could investigate the combined effects of resistance training and a specific dietary intervention on muscle mass, secretome composition, and epigenetic markers in individuals with early-stage Alzheimer's disease. This type of research could provide valuable insights into the potential of lifestyle interventions to modify disease progression. We urge increased funding and resources for clinical research focused on muscle in metabolic and neurodegenerative diseases. Research priorities should include personalized exercise interventions, combined exercise and nutritional strategies, and pharmacological modulation of the secretome and epigenome. This research holds immense promise for developing novel and effective treatments for these debilitating conditions. Muscle plays a pivotal role in systemic health and disease. By targeting the muscle secretome, epigenetics, and atrophy, we can unlock innovative therapeutic avenues. A collaborative effort among researchers, clinicians, and policymakers is crucial to advance this field and translate research findings into tangible clinical benefits. We call on all stakeholders to join us in this critical endeavor. Future studies should elucidate how specific exercise-induced secretome

profiles interact with epigenetic modifications to counteract muscle atrophy in neurodegenerative contexts.

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