International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn25S405

Muscle regeneration and increased muscle mass in athletes under the modulation of microRNAs and exosomes: a systematic review

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DOI: https://doi.org/10.54448/ijn25S405
Received: 09-05-2025; Revised: 10-31-2025; Accepted: 11-12-2025; Published: 11-19-2025; IJN-id: e25S405

Editor: Dr. Fernando Alberto Carrasco Naranjo, MD, MSc, MPH.

Abstract

Introduction: In the context of muscle regeneration, precise nutrition makes it possible to recover from muscle injuries in athletes. Muscle wasting results in reductions in basal muscle protein synthesis and muscle resistance to anabolic stimulation. Therefore, higher protein intakes are necessary. Regular physical training associated with nutritional health has broad benefits to the health of the gut microbiota. MicroRNAs (miRs) and exosomes have emerged as critical regulators of numerous biological processes, modulating gene expression at the post-transcriptional level. **Objective:** A systematic review of the literature was developed to highlight the process of muscle regeneration and increased muscle mass in athletes under the modulation of microRNAs and exosomes. **Methods:** The systematic review rules of the PRISMA Platform and the methodological quality of AMSTAR-2 were followed. The research was carried out from May to June 2025 in the Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 134 articles were found, and 62 articles were evaluated in full and 52 were included and developed in this systematic review study. Clinical studies showed homogeneity in their results, with Chi-Square (X^2) =75.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies with a high risk of bias and 20 studies that did not meet GRADE and AMSTAR-2. miRs play an important role as regulatory molecules during the muscle healing process. Myoblasts are known to secrete exosomes enriched with miRs into the inflammatory environment, whereby miR-224 is transferred to macrophages to inhibit M2 polarization. Additional data demonstrate that WNT-9a may be a direct target of miR-224 for macrophage polarization.

The results showed that miR-122 and myogenic markers were downregulated in C2C12 cells after TGF-β stimulation, and overexpression of miR-122 can restore myogenesis inhibited by TGF-β. Evidence suggests that the exosome derived from mesenchymal stem cells exhibits functions similar to mesenchymal stem cells with low immunogenicity and without tumorization. High rates of intestinal self-renewal are enabled by intestinal stem cells (LGR5+) at the base of intestinal crypts. LGR5+ activity, including proliferation and differentiation rates, is affected by large shifts in nutrient availability, as occurs on a high-fat diet or fasting. The practice of physical activity, endogenous metabolites, and dietary nutrients can directly influence epigenetic enzymes. Dietary manipulations and metabolites can affect tissue stem cell fate decisions. Selfrenewal and differentiation of mesenchymal stem cells can be regulated by manipulating vitamin C, A, or D levels and valine restriction.

Keywords: Muscle regeneration. Muscle mass. Athletes. Metabolomics. microRNAs. Exosomes. Nutrients.

Introduction

In the context of muscle regeneration, precise nutrition enables the recovery of muscle injuries in athletes. Injuries result in reduced participation in sports and decreased physical activity. After an injury, an inflammatory response is initiated, and although excessive inflammation can be detrimental, given the importance of the inflammatory process for wound healing, attempting to drastically reduce inflammation may not be ideal for optimal recovery **[1,2]**.

In this respect, muscle loss results in reductions in basal muscle protein synthesis and muscle resistance to anabolic stimulation. Energy balance is compromised. Thus, higher protein intakes (2-2.5 g/kg/day) are necessary. In this context, there is promising evidence for the use of omega-3 fatty acids and creatine to combat muscle loss and increase hypertrophy. The primary nutritional recommendation for injured exercise practitioners is to consume a well-balanced diet based on minimally processed whole foods or ingredients derived from whole foods **[2,3]**.

These investigations typically assess the performance limits or health benefits resulting from exercise **[4]**. Thus, recent progress has been made regarding the gut microbiota, regenerative nutrition, and skeletal muscle metabolism **[4-6]**. In this context, regular physical training associated with nutritional health has broad benefits for the health of the gut microbiota, acting positively on almost all organ systems of the body **[7-9]**.

In this sense, microRNAs (miRs) have emerged as critical regulators of numerous biological processes, modulating gene expression at the post-transcriptional level. The discovery of miRNAs as new and important regulators of gene expression has broadened the biological understanding of the regulatory mechanism in muscle **[10]**. miRs are a unique subset of non-coding RNA, whose primary function is to post-transcriptionally modulate gene expression **[11]**. Most miRs are transcribed from nuclear DNA in a similar way to other mRNAs: by the polymerase II enzyme. miRs can be transcribed individually or in clusters, and may have their own promoter **[12-14]**.

In addition, adult stem cells (ASCs) stand out, such as intestinal stem cells at the base (crypts) of the intestine and muscle stem cells outside the sarcolemma next to the muscle basement membrane **[15-17]**. The tissue niche is also capable of influencing the metabolism of ASCs. The metabolism of tissue stem cells has been concentrated on central carbon metabolism, that is, the generation of metabolic building blocks via glycolysis, oxidative phosphorylation, or the pentose phosphate pathway. In this sense, ASCs mediate the homeostasis and regeneration of tissues and organs, making decisions about whether to remain quiescent, proliferate, or differentiate into mature cell types. These decisions are directly integrated with the energy balance and nutritional status of the organism. Metabolic byproducts and substrates that regulate epigenetic and signaling pathways are considered to have an instructive, rather than observer, role in regulating cell fate decisions **[17]**.

In this context, growing evidence suggests that metabolism during quiescence, activation, and differentiation can vary between tissues, integrating signaling cues and metabolic inputs from the niche and the organism as a whole, mainly through nutrient signaling and the gut microbiota **[18-25]**.

Therefore, the present study developed a systematic literature review to highlight the process of muscle regeneration and muscle mass increase in athletes under the modulation of microRNAs and exosomes.

Methods

Study Design

This study followed an international model for systematic review, following the PRISMA (Preferred Reporting Items for systematic reviews and meta-analysis) guidelines **[26]** and the AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards **[27]**.

Data Sources and Search Strategy

The search strategies for this systematic review were based on the keywords (DeCS/MeSH Terms): *"Muscle regeneration. Muscle mass. Athletes. Metabolomics. microRNAs. Exosomes. Nutrients".* The search was conducted from May to June 2025 in the Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar databases. In addition, a combination of keywords with the booleans "OR", "AND", and the operator "NOT" was used to target scientific articles of interest.

Study Quality, Eligibility Criteria, and Risk of Bias

Studies were selected that rigorously presented the results of the search process and demonstrated scientific quality according to the GRADE classification, and that did not present a significant risk of bias, i.e., that could compromise the reliability of the results. According to GRADE recommendations **[28]**, the quality of scientific evidence in the studies addressed was classified as high, moderate, low, or very low, according to the risk of evidence bias, sample size, clarity of comparisons, precision, and consistency in the effects of the analyses. High quality of evidence was attributed through four criteria: 1) Randomized or prospective controlled clinical trials; 2) Retrospective clinical trials or case series; 3) Sample size greater than 15 participants; 4) Studies with statistically Well-constructed results; 5) Studies published in indexed journals with a significant impact factor; 6) descriptive, interpretative, theoretical (credibility of methods), and pragmatic validity.

The Cochrane Instrument **[29]** was adopted to assess the risk of bias of the selected studies by means of the Cohen Test to calculate the effect size (Effect Size) versus the Inverse of the Standard Error (precision or sample size) to determine the Risk of Bias of the studies by means of the Funnel Plot graph.

Results and Discussion

Summary of Literature Findings

134 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated, and a further exclusion was made, removing articles that did not include the theme of this article, resulting in 94 articles. After excluding articles that did not meet the methodological quality criteria recommended by AMSTAR-2, a total of 62 articles were evaluated in full, and 52 were included and developed in this systematic review study (Figure 1). Of the total of 56 articles, 4 articles are related to the PRISMA, GRADE, COCHRANE, and AMSTAR-2 standards, and were not considered for inclusion in the scientific writing. The clinical studies showed homogeneity in their results, with Chi-Square (X^2)=75.5% > 50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies with a high risk of bias and 20 studies that did not meet the GRADE and AMSTAR-2 criteria.

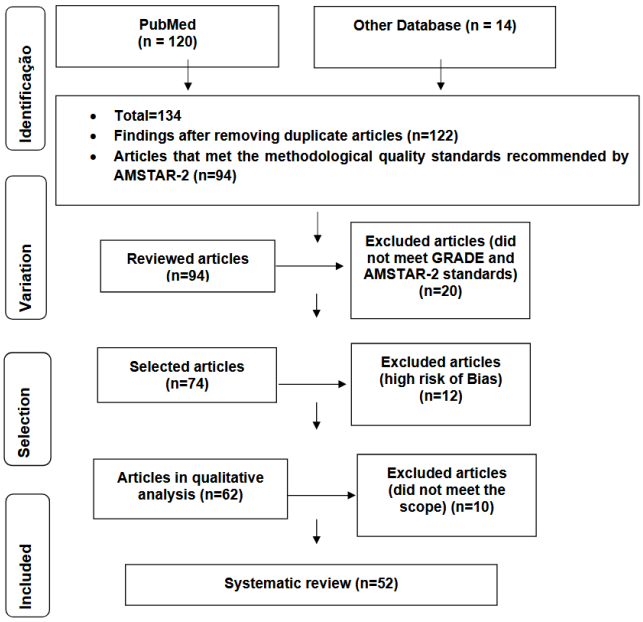

Figure 1. Flowchart showing the article selection process. Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's d test. The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) shown at the base of the graph and in studies with large sample sizes shown in the upper region.

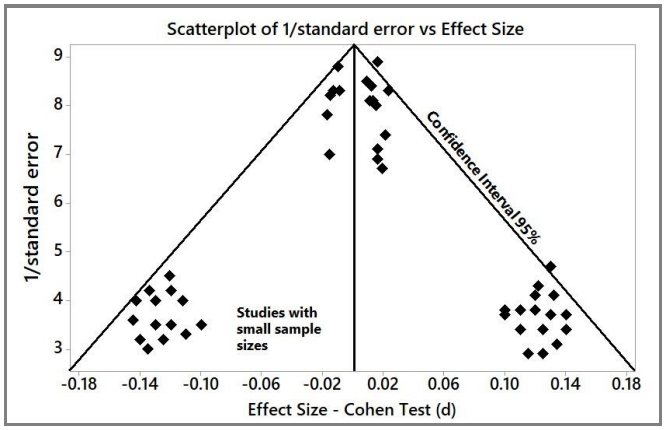

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies shown at the bottom of the graph. Studies with high

confidence and high recommendation are shown above the graph (NTotal = 52 clinical studies fully assessed in the systematic review). Source: Own authorship.

MicroRNAs/Exosomes - Main Approaches and Clinical Outcomes

MicroRNAs (miRs) are small regulatory RNA transcripts capable of post-transcriptionally silencing mRNA messages. miRs are involved in regulating cellular processes by producing, eliminating, or repairing damage caused by reactive oxygen species, and are active players in redox homeostasis. Increased mitochondrial biogenesis, function, and hypertrophy of skeletal muscle are important adaptive responses to regular exercise. There are redox-sensitive regulatory functions of miRs **[30]**.

In this respect, it is noteworthy that severe inflammation and disruption of myogenic differentiation are the main obstacles to skeletal muscle healing after injury. miRs play an important role as regulatory molecules during the muscle healing process, but the detailed mechanism of miR-mediated intercellular communication between myoblasts and macrophages remains obscure. It is known that myoblasts secrete miRenriched exosomes in the inflammatory environment, through which miR-224 is transferred to macrophages to inhibit M2 polarization. Additional data demonstrate that WNT-9a may be a direct target of miR-224 for macrophage polarization. In turn, the secretome of M1 macrophages impairs myogenic differentiation and promotes proliferation. The elevation of exosome-derived miR-224 is caused by the activation of the key factor E2F1 in myoblasts and demonstrates the RB/E2F1/miR-224/WNT-9a axis. In vivo results have shown that treatment with antagomir-224 or liposomes containing miR-224 inhibitors suppresses fibrosis and improves muscle recovery **[31]**.

In addition, it has been discovered that the transforming growth factor-β (TGF-β)/Smad pathway plays an important role in inhibiting myogenesis, a fundamental stage in skeletal muscle regeneration. It has also been shown that microRNA-122-5p (miR-122) functions to negatively regulate the TGF-β/Smad pathway. miR-122 may also be involved in the process of skeletal muscle myogenesis through the regulation of the TGF-β/Smad pathway. In this sense, a study investigated the impact of miR-122 on skeletal muscle myogenesis and explored its underlying mechanism. The results showed that miR-122 and myogenic markers were negatively regulated in C2C12 cells after TGF-β stimulation, and miR-122 overexpression can restore TGF-β-inhibited myogenesis. Furthermore, it was discovered that the effect of miR-122 overexpression could be rescued by TGFBR2 overexpression **[32]**.

A study evaluated the impact of different exercise modalities on the plasma concentration of miRNA-126, as a marker of endothelial damage. The plasma concentration of miRNA-126 and miRNA-133 (a marker of muscle damage) was assessed by qRT-PCR analysis in plasma samples from healthy individuals performing one of the following exercise tests: (1) symptom-limited maximal exercise test, (2) cycling for 4 hours, (3) running a marathon, and (4) resistance exercise. A symptom-limited maximal exercise test resulted in a significant increase in circulating miRNA-126 at maximum power (2.1 times versus baseline), while the concentration of miRNA-133 remained unchanged. In line, four hours of cycling increased plasma miRNA-126 concentration with a maximum 30 minutes after onset (4.6 times versus baseline) without impacting miRNA-133 concentration. Finishing a marathon increased both miRNA-126 and miRNA-133. In contrast, eccentric endurance training led to an isolated increase in miRNA-133 level (2.1 times versus baseline) with miRNA-126 unchanged **[33]**.

Main Cellular and Molecular Processes of Regeneration

In this scenario, adult stem cells, such as mesenchymal stem cells (MSCs), stand out as an alternative for cell therapy and human tissue engineering, since they have been found to have a high degree of plasticity, with the capacity for self-renewal and differentiation into specialized progenitors **[34]**. In this respect, MSCs are primordial mesodermal cells present in all tissues and are capable of differentiating in vitro and in vivo into different cell types. Their therapeutic potential is mainly explained by the production of bioactive molecules, which provide a regenerative microenvironment in injured tissues **[35]**.

MSCs secrete a cascade of cytokines and growth factors with paracrine, autocrine, and endocrine activities, such as IL-6, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15, macrophage colony-stimulating factor (M-CSF), Flt-3 ligand and stem cell factor (SCF), leukaemia inhibitory factor (LIF), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). When conjugated, these factors can produce a series of responses from the local immune system, stimulating angiogenesis and inducing the proliferation and differentiation of mesenchymal stem cells in the desired tissue **[36]**.

MSCs induce the expression of junction proteins and increase microvascular integrity and nitric oxide (NO) production by macrophages **[35]**. The vascular

stromal fraction (VSF) originating from MSCs is a heterogeneous mixture of cells, including fibroblasts, pericytes, endothelial cells, blood cells, and adipose derived mesenchymal stem cells (ADSCs).

Exosomes stand out along with ADSCs. Exosomes are extracellular vesicles with a diameter of 40-100 nm and a density of 1.13-1.19 g/mL, containing proteins, mRNAs, miRNAs, and DNAs. Exosomes change the biochemical characteristics of recipient cells by delivering biomolecules and play a role in cell communication. These vesicles are produced from body fluids and different cell types. Evidence suggests that ADSC-derived exosomes (ADSC-EXO) exhibit functions similar to ADSC with low immunogenicity and no tumorization **[37]**.

In this regard, the composition of exosomes differs based on their sources. The protein and lipid content of exosomes was measured by several methods, such as fluorescence-activated cell selection, Western blotting, mass spectrometry, and immunoelectron microscopy. In this respect, Rabs and Annexin, including Annexin I, II, V, and VI, are cytosolic proteins present in exosomes that contribute to exosome docking formation, membrane fusion, and kinetic regulation of cytoskeletal membranes. In addition, adhesion molecules such as intercellular adhesion molecule-1, CD11a, CD11b, CD11c, CD18, CD9 adipose tissue globule EGF-factor VIII (MFG-E8), CD58, CD146, CD166 have also been identified in exosomes **[38]**. Exosomes also contain heat shock proteins (Hsp70 and Hsp90), which facilitate the loading of peptides into MHC I and II **[39,40]**.

Exosomes contain non-coding RNAs or fragments, including overlapping RNA transcripts, protein-coding regions, structural RNAs, transfer RNA fragments, YRNAs, short hairpin RNAs, small interfering RNAs (siRNAs), microRNA (miRNA), messenger RNA (mRNA), and DNA **[41]**. Regarding miRNA, exosomes have miR-1, miR-15, miR-16, miR-17, miR-18, miR-181, and miR-375 **[42]**. In addition, several cytokines, such as Tumour Necrosis Factor-α (TNF-α), Granulocyte Macrophage Colony Stimulating Factor (GMCSF), Interleukin (IL)-2, IL-6, IL-8, IL-10, IL-15, IL-1β, are expressed in exosomes **[43]**.

These biological signals attract bone-forming cells to the recipient site. Growth factors and other proteins are some biological signals that may be involved in bone neoformation and tissue remodeling. In addition, through chemotaxis, there is migration of bone-forming cells to the application area, as stimulation of cell migration occurs in response to chemical stimuli **[44-46]**.

Crosstalk - Skeletal Muscle, Nutrients and Regenerative Processes

Metabolism encompasses the interactions between diet, the microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to maintain life. The small intestine, comprising the duodenum, jejunum, and ileum, is the organ that self-renews most rapidly in humans. The small intestine exhibits specific metabolites with higher levels of fatty acid oxidation occurring in the upper part of the small intestine and decreasing distally towards the ileum **[15,16]**. High rates of intestinal self-renewal are enabled by intestinal stem cells (LGR5+) at the base of the intestinal crypts **[16]**. Cells in the intestine can communicate via metabolic signals, with differentiated Paneth cells secreting lactate to support LGR5+ function **[15,46]**.

In this sense, the balance between LGR5+ and differentiated cell fate can also be affected by intrinsic changes to the cell in central carbon metabolism. The mitochondrial pyruvate carrier (MPC), comprising the MPC1 and MPC2 subunits, is required for pyruvate oxidation between species, allowing pyruvate to enter the mitochondria. Genetic deletion of the MPC1 subunit or inhibition of MPC distorts cellular metabolism towards glycolysis and increases LGR5+ proliferation. Overexpression of MPC1/MPC2 reduces the activity of LGR5+ **[15,16,24]**.

A recent study demonstrated that the expression of the enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2), which regulates the ratio-limiting step in ketone body synthesis, is enriched in LGR5+. Loss of Hmgcs2 impairs regeneration and promotes promiscuous differentiation into the Paneth cell line. The ketone body β-hydroxybutyrate inhibits class I histone deacetylases to increase transcriptional activation of Notch signaling and maintain stem cell self-renewal **[24]**.

The intestine constantly contains nutrients derived from the diet and is therefore responsive to different types of nutrients **[14]**. For example, studies conducted on normal and patient-derived tumor intestinal organoids have demonstrated that vitamin D levels can change the balance between stem cell fates, as well as their differentiation **[1,2]**. Therefore, the activity of LGR5+, including proliferation and differentiation rates, is affected by large deviations in nutrient availability, such as occurs in a high-fat diet or fasting. Physical activity, endogenous metabolites, and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter cell fate by controlling chromatin accessibility and downstream gene expression patterns **[24]**.

Thus, many substrates and cofactors for

chromatin-modifying enzymes are derived from metabolic pathways involving the tricarboxylic acid cycle, the methionine cycle, the folate cycle, glycolysis, β-oxidation, and the hexosamine pathway. These metabolites can serve as activators or inhibitors of epigenetic writers, such as proteins containing the Jumonji C domain (JmjC), DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), ten-eleven translocase DNA demethylases (TETs), and histone deacetylases (HDACs). In this sense, metabolites can influence nutrient-sensing signaling pathways **[24]**.

Thus, the mechanistic target of rapamycin complex 1 (mTORC1) can be activated by growth factor-induced signaling only when the amino acids arginine and leucine, as well as the cofactor S-adenosylmethionine (SAM), are detected within the cell. In addition, the energy balance communicated through the cellular AMP/ADP-ATP ratio can be detected by AMP-activated protein kinase (AMPK). Furthermore, transcription factors can be directly regulated by metabolites; for example, the tryptophan metabolite kynurenine is an endogenous agonist of the aryl hydrocarbon receptor, and alpha-ketoglutarate (α-KG) binds to and activates IKKβ and initiates NF-κβ signaling **[47]**.

In this scenario, dietary manipulations and metabolites can affect the fate decisions of tissue stem cells, as highlighted in the small intestine (intestinal stem cells (LGR5+)), hematopoietic system (hematopoietic stem cells (HSCs)), liver, muscle (muscle stem cells/satellite cells), and hair follicles (hair follicle stem cells (HFSCs)). For example, in HFSCs, mitochondrial pyruvate carrier 1 (MPC1) and lactate dehydrogenase (LDHA) regulate the balance between telogen and anagen during the hair cycle. In LGR5+, 3-hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2) is highly expressed, while MPC1/2 are expressed at low levels. The ketogenic or high-glucose diet regulates the balance of LGR5+ self-renewal. Self-renewal and HSC differentiation can be regulated by manipulating vitamin C, A, or D levels and by restricting valine **[47]**.

Regarding muscle regeneration, a diet rich in nicotinamide riboside can increase the number of muscle stem cells and function in a histone deacetylase (SIRT1)-dependent manner. Muscle stem cells, called satellite cells, are responsible for maintaining adult muscle mass and repairing after injury. Several studies have demonstrated how changes in innate metabolism interfere with the differentiation of satellite stem cells into mature myocytes **[15]**. For example, single-cell mapping with histone acetylation showed that acetylation levels tend to be low in quiescent cells.

A study found that isolated quiescent muscle stem cells express fatty acid oxidation enzymes/transporters; however, as they exit quiescence and enter the cell cycle for proliferation, a metabolic transition occurs to favor glycolysis **[15,16]**. In this sense, SIRT1 is a target of enhanced glycolysis. SIRT1 represses the maturity expression of skeletal muscle-specific genes, as well as genes involved in mitochondrial biogenesis.

Enhanced glycolysis depletes NAD+, an essential metabolic cofactor of SIRT1, reducing SIRT1 activity and promoting downstream activation of these mature muscle-specific genes and differentiation **[15]**.

Metabolic pathways and chromatin modifications are closely linked, and therefore, many changes in metabolism influence epigenetic changes and alter gene expression. For example, signaling pathways including mTORC, AMPK, MAPK, and others are all sensitive to changes in nutrient levels. In addition, transcription factors are directly regulated by metabolites. Furthermore, it is possible that the transcriptional machinery itself also responds to nutrients, for example, RNA polymerase II is modified by O-GlcNAc, a metabolite derived from the hexosamine biosynthesis pathway **[48-50]**.

Finally, epigenetic signaling pathways and transcription are affected by changes in nutrient levels. In addition, a focus of the literature on stem cell metabolism is centered on central carbon metabolism and the balance between glycolysis and oxidative phosphorylation in the regulation of cell fate **[50,51]**. Therefore, future research defining the dietary and metabolic control of cell fate decisions in muscle tissues will be of great importance in the fields of metabolism and regenerative medicine **[52-56]**.

Conclusion

It was concluded that microRNAs play an important role as regulatory molecules during the muscle healing process. Myoblasts are known to secrete microRNA-enriched exosomes in the inflammatory environment, through which miR-224 is transferred to macrophages to inhibit M2 polarization. Additional data demonstrate that WNT-9a may be a direct target of miR-224 for macrophage polarization. The results showed that miR-122 and myogenic markers were downregulated in C2C12 cells after TGF-β stimulation, and miR-122 overexpression can restore TGF-β-inhibited myogenesis. Evidence suggests that exosomes derived from mesenchymal stem cells exhibit functions similar to mesenchymal stem cells with low immunogenicity and no tumorization. High rates of intestinal self-renewal are enabled by intestinal stem cells (LGR5+) at the base of the intestinal crypts. The activity of LGR5+, including proliferation and

differentiation rates, is affected by large deviations in nutrient availability, such as occurs in high-fat diets or fasting. Physical activity, endogenous metabolites, and dietary nutrients can directly influence epigenetic enzymes. Dietary manipulations and metabolites can affect the fate decisions of tissue stem cells. Self-renewal and differentiation of mesenchymal stem cells can be regulated by manipulating vitamin C, A, or D levels and by restricting valine.

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Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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