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

REVIEW ARTICLE

DOI: 10.54448/ijn25202

Nutrological triggers of muscle regeneration in athletes under modulation and gene expression of microRNAs and exosomes: a systematic review

Frederico Teixeira Izidorio[1*], Márcia Cavalheiro Alves[2], Mateus Antunes Nogueira[3], Hugo Menezes Lopes[4], Ricardo de Oliveira Carvalho[5], Ana Claudia Santana Cano[6], Vittor Cândido Soares[7], Juliana da Silva Pereira[8], Marília de Andrade Salvá[9], Thamyres Veras Alves[10]

[1] Araxá emergency care unit. Av João Paulo II, 1900. Araxá, Minas Gerais, Brazil.
[2] Diagnosis Medical Imaging Clinic Setor C North CNC 1 s/n Lots 10/11. Taguatinga. Brasília, Distrito Federal, Brazil.
[3] Active Life Teaching and Research (Vida Ativa Ensino e Pesquisa). Street: Paes Leme, 215, conjunto 307, Zip code: 05424-150, Pinheiros, São Paulo, Brazil.
[4] Nossa Senhora das Graças Hospital. Street: Visconde de Jequitinhonha, 1144, Boa Viagem, Recife, Pernambuco, Brazil.
[5] University Hospital-UFPI University Campus Minister Petrônio Portela, s/n - Ininga, Teresina, Piauí, Brazil.
[6] Auxiliadora Hospital. Avenue Rosario Congro, 1533, Colinos, Três Lagoas, Mato Grosso do Sul, Brazil.
[7] Hospital da Mulher Mãe Luzia. Obstetric ICU. Avenue Fab, 81 - Central, Macapá, Amapá, Brazil.
[8] Livia Hasegawa Clinic. Street: Manoel da Nobrega, 354, cj 16 Paraiso, São Paulo, Brazil.
[9] Medradius Oncological Hospital. Street: Hugo Corrêa Paes, 104, Gruta de Lourdes, Maceió, Alagoas, Brazil.
[10] Pelopidas Silveira Hospital, 232, km 6, Curado, Recife, Pernambuco, Brazil.

*Corresponding author: Dr. Frederico Teixeira Izidorio.
Araxá emergency care unit. Av João Paulo II, 1900.
Araxá, Minas Gerais, Brazil.
E-mail: fredericoizidorio@hotmail.com

DOI: https://doi.org/10.54448/ijn25202
Received: 12-19-2024; Revised: 03-03-2025; Accepted: 03-17-2025; Published: 03-21-2025; IJN-id: e25202

Editor: Dr. Idiberto José Zotarelli-Filho, MSc, Ph.D., Post-Doctoral.

Abstract

Introduction: In the context of regenerative nutrological processes, 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 (2-2.5 g/kg/day) 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 was conducted to demonstrate, through scientific studies, the nutrological triggers of muscle regeneration in athletes under the modulation and gene expression of microRNAs and exosomes. **Methods:** The systematic review rules of the PRISMA Platform and the methodological quality of AMSTAR were followed. The research was carried out from June to August 2024 in the Web of Science, Scopus, 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 =72.4%>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. 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 miR224 for macrophage polarization. The results showed that miR-122 and myogenic markers were down-regulated 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. Self-renewal and differentiation of mesenchymal stem cells can be regulated by manipulating vitamin C, A, or D levels and valine restriction.

Keywords: Nutrology. Muscle regeneration. Athletes. Metabolism. microRNAs. Exosomes.

Introduction

In the context of nutritional regenerative processes, nutrition facilitates 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 regard, muscle loss results in reductions in basal muscle protein synthesis and muscle resistance to anabolic stimulation. Energy balance is compromised. Therefore, 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 main nutritional recommendation for injured exercisers should be to consume a well-balanced diet based on minimally processed whole foods or ingredients made from whole foods **[2,3]**.

These investigations usually assess performance limits or exercise-induced health benefits **[4]**. Thus, recent progress has been made in 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, positively acting 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 novel and important regulators of gene expression has expanded the biological understanding of the regulatory mechanism in muscle **[10]**. MiRs are a unique subset of non-coding RNA whose primary function is to modulate gene expression post-transcriptionally **[11]**. Most miRNAs are transcribed from nuclear DNA like other mRNAs: by the polymerase II enzyme. MiRs can be transcribed individually or in clusters and may have their 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 basement membrane of the muscle **[15-17]**. The tissue niche is also capable of influencing ASC metabolism. The metabolism of tissue stem cells has been focused 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, increasing evidence suggests that metabolism during quiescence, activation, and differentiation may vary between tissues, integrating signaling cues and metabolic inputs from the niche and the organism as a whole, mainly through nutrient and intestinal microbiota signaling **[18-25]**.

Given this, the present study performed a systematic review to demonstrate, through scientific studies, the nutrological triggers of muscle regeneration in athletes under the modulation and gene expression of microRNAs and exosomes.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules **[26]** and the AMSTAR (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. Athletes. Metabolism. Metabolomics. microRNAs. Exosomes. Nutrients*. The search was conducted from June to August 2024 in the

Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar databases. In addition, a combination of the keywords with the Boolean terms "OR", "AND" and the operator "NOT" were used to target the scientific articles of interest.

Quality of Studies, Eligibility Criteria, and Risk of Bias

Studies that rigorously presented the results of the search process that presented scientific quality according to the GRADE classification, and that did not present a significant risk of bias, that is, that could compromise the safety of the results, were selected.

According to the GRADE recommendations **[28]**, the quality of the scientific evidence in the studies addressed was classified as high, moderate, low, or very low, according to the risk of bias of evidence, 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 well-designed statistical results; 5) Studies published in indexed journals and with a significant impact factor; 6) descriptive, interpretative, theoretical (credibility of methods) and pragmatic validity.

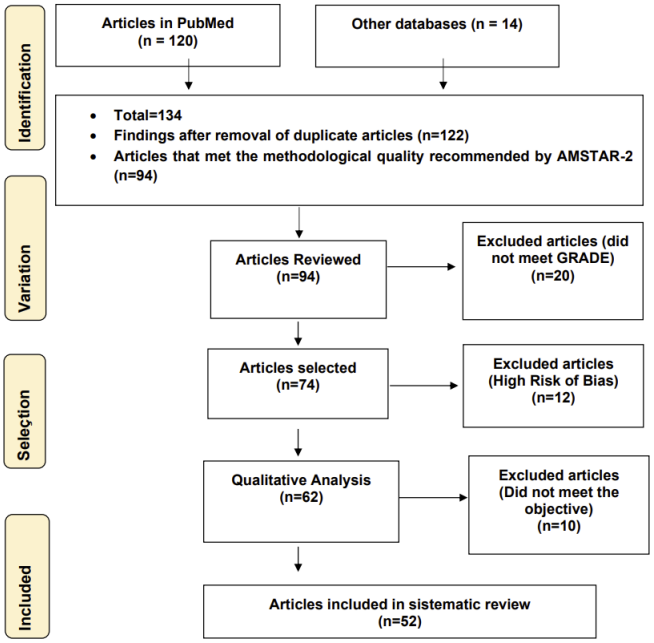
The Cochrane Instrument **[29]** was adopted to assess the risk of bias of the selected studies using the Cohen's Test to calculate the effect size versus the Inverse of the Standard Error (precision or sample size) to determine the Risk of Bias of the studies using the Funnel Plot graph.

Results and Discussion

Summary of Literature Findings

A total of 134 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 94 articles. After the exclusion of articles for not meeting the methodological quality criteria recommended by AMSTAR, a total of 62 articles were evaluated in full and 52 were included and developed in the present systematic review study (Figure 1). Of the total of 56 articles, 4 articles are related to the PRISMA, GRADE, COCHRANE, and AMSTAR standards, and were not considered for composing the scientific writing. The clinical studies presented homogeneity in their results, with Chi-Square X^2 =72.4%>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.

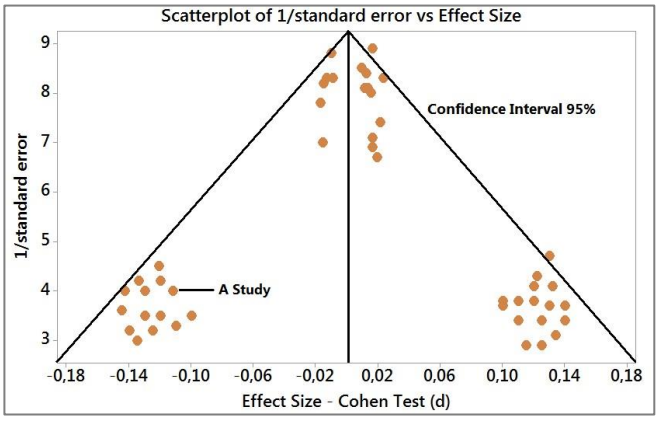
Figure 1. Flowchart showing the article selection process.



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 Test (d). 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 among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are shown in the upper region.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample size that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (NTotal=52 clinical studies evaluated in full in the systematic review).



Source: Own authorship.

Main Clinical Approaches and Outcomes

MicroRNAs (miRs) are small regulatory RNA transcripts capable of post-transcriptionally silencing mRNA messages. miRs are involved in the regulation of 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. Redox-sensitive regulatory functions of miRs are present **[30]**.

In this regard, it is noteworthy that severe inflammation and impaired 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 unclear. Myoblasts are known to secrete miR-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. In turn, the M1 macrophage secretome impairs myogenic differentiation and promotes proliferation. The elevation of exosome-derived miR-224 is caused by 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, the transforming growth factor-β (TGF-β)/Smad pathway has been found to play an important role in inhibiting myogenesis, a key stage in skeletal muscle regeneration. MicroRNA-122-5p (miR-122) has also been shown to negatively regulate the TGF-β/Smad pathway. MiR-122 may also be involved in the process of skeletal muscle myogenesis by regulating the TGF-β/Smad pathway. In this regard, 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 downregulated in C2C12 cells after TGF-β stimulation and overexpression of miR-122 could restore myogenesis inhibited by TGF-β. Furthermore, it was found that the effect of miR-122 overexpression could be rescued by TGFBR2 overexpression **[32]**.

Furthermore, 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) 4-h cycling, (3) marathon running, and (4) endurance exercise. A symptom-limited maximal exercise test resulted in a significant increase in circulating miRNA-126 at maximal power (2.1-fold versus baseline), while miRNA-133 concentration remained unchanged. In line, four hours of cycling increased plasma miRNA-126 concentration with a maximum of 30 min after start (4.6-fold versus baseline) with no impact on 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-fold versus baseline) with unchanged miRNA-126 **[33]**.

Main Cellular and Molecular Processes of Regeneration

In this scenario, adult stem cells, such as mesenchymal stem cells (MSCs), are an alternative for cell therapy and human tissue engineering, since it has been found that they have a high degree of plasticity, with the capacity for self-renewal and differentiation into specialized progenitors **[34]**. In this aspect, 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]**.

Furthermore, 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), leukemia inhibitory factor (LIF), granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). These factors, when combined, 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]**.

In addition, MSCs induce the expression of junction proteins and increase microvascular integrity and nitric oxide (NO) production by macrophages **[35]**. The stromal vascular fraction (SVF) from MSCs is a heterogeneous mixture of cells, including fibroblasts, pericytes, endothelial cells, blood cells, and adipose-derived mesenchymal stem cells (ADSC).

Also, exosomes stand out along with ADSC. Exosomes are extracellular vesicles measuring 40–100 nm in diameter and with a density of 1.13–1.19 g/mL, containing proteins, mRNAs, miRNAs, and DNAs. Exosomes change the biochemical characteristics of

recipient cells through the delivery of biomolecules and play a role in cellular communication. These vesicles are produced from body fluids and different cell types. Evidence suggests that ADSC-derived exosome (ADSC-EXO) exhibits similar functions to ADSC with low immunogenicity and no tumorigenesis **[37]**.

In this regard, the composition of exosomes differs based on their sources. The protein and lipid content of exosomes was measured by various methods such as fluorescence-activated cell sorting, Western blotting, mass spectrometry, and immunoelectron microscopy. In this regard, Rabs and Annexin, including Annexin I, II, V, and VI, are cytosolic proteins present in exosomes that contribute to the formation of exosome docking, 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 (AGM-E8), CD58, CD146, and CD166 have also been identified in exosomes **[38]**. Exosomes also contain heat shock proteins (Hsp70 and Hsp90), which facilitate the loading of peptides onto MHC I and II **[39,40]**.

Exosomes contain non-coding RNAs or fragments, including overlapping RNA transcripts, protein-coding region, structural RNAs, transfer RNA fragments, YRNAs, short hairpin RNAs, small interfering RNAs (siRNAs), microRNA (miRNA), messenger RNA (mRNA), and DNA **[41]**. Regarding miRNA, exosomes contain miR-1, miR-15, miR-16, miR-17, miR-18, miR-181, and miR-375 **[42]**. In addition, several cytokines, such as Tumor 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 new bone formation and tissue remodeling. In addition, through chemotaxis, there is migration of bone-forming cells to the application area, since 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, microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to sustain life. The small intestine, comprising the duodenum, jejunum, and ileum, is the most rapidly self-renewing organ in humans. The small intestine exhibits specific metabolic pathways 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 the LGR5+ function **[15,46]**.

In this sense, the balance between LGR5+ and differentiated cell fate may also be affected by cell-intrinsic changes in central carbon metabolism. The mitochondrial pyruvate carrier (MPC), comprising the MPC1 and MPC2 subunits, is required for interspecies oxidation of pyruvate, allowing pyruvate entry into mitochondria. Genetic deletion of the MPC1 subunit or inhibition of MPC biases cellular metabolism toward glycolysis and increases LGR5+ proliferation. Overexpression of MPC1/MPC2, on the other hand, reduces LGR5+ activity **[15,16,24]**.

A recent study demonstrated that the expression of the enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2), which regulates the rate-limiting step in ketone body synthesis, is enriched in LGR5+. Loss of Hmgcs2 impairs regeneration and promotes promiscuous differentiation toward the Paneth cell lineage. The ketone body βhydroxybutyrate inhibits class I histone deacetylases to enhance transcriptional activation of Notch signaling and maintain stem cell self-renewal **[24]**. Furthermore, the intestine is constantly supplied with dietary nutrients and is therefore nutrient-responsive **[14]**. For example, studies in normal and tumor-derived intestinal organoids have shown that vitamin D levels can shift the balance between stem cell fates and differentiation **[1,2]**. Thus, LGR5+ activity, including proliferation and differentiation rates, is affected by large shifts in nutrient availability, such as high-fat diet or fasting. Physical activity, endogenous metabolites, and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications to 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 Jumonji C (JmjC) domain-containing proteins, 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-adenosyl methionine (SAM), are sensed within the cell. Furthermore, the energy balance communicated through the cellular AMP/ADP-ATP ratio can be sensed 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 alphaketoglutarate (α-KG) binds to and activates IKKβ and initiates NF-κβ signaling **[47]**.

In this scenario, dietary manipulations and metabolites may affect tissue stem cell fate decisions, 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 is expressed at low levels. A ketogenic or high-glucose diet regulates the balance of LGR5+ self-renewal. HSC self-renewal and differentiation can be regulated by manipulating vitamin C, A, or D levels and by valine restriction **[47]**.

Regarding muscle regeneration, a diet rich in nicotinamide riboside can increase muscle stem cell numbers and function in a histone deacetylase (SIRT1)-dependent manner. Muscle stem cells, termed satellite cells, are responsible for maintaining adult muscle mass and repair after injury. Several studies have demonstrated how changes in innate metabolism interfere with satellite stem cell differentiation into mature myocytes **[15]**. For example, single-cell histone acetylation mapping has shown that acetylation levels tend to be low in quiescent cells. In this context, 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 increased glycolysis. SIRT1 represses the expression of maturity-specific skeletal muscle genes, as well as genes involved in mitochondrial biogenesis. Enhanced glycolysis depletes NAD+, a key metabolic cofactor of SIRT1, reducing SIRT1 activity and promoting downstream activation of these mature muscle-specific genes and differentiation **[15]**.

Thus, metabolic pathways and chromatin modifications are intimately 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. Furthermore, 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]**.

Thus, epigenetic signaling pathways and transcription are affected by changing nutrient levels. Furthermore, a focus of the literature on stem cell metabolism has centered on central carbon metabolism and the balance between glycolysis and oxidative phosphorylation in regulating 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. It is known that myoblasts secrete microRNA-enriched exosomes in the inflammatory environment, through which miR-224 is transferred to macrophages to inhibit M2 polarization. Further 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 could restore TGF-β-inhibited myogenesis. The evidence suggests that mesenchymal stem cell-derived exosome exhibits mesenchymal stem cell-like functions with low immunogenicity and no tumorigenesis. 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, such as high-fat diet or fasting. Physical activity, endogenous metabolites, and dietary nutrients can directly influence epigenetic enzymes. Dietary manipulations and metabolites can affect tissue stem cell fate decisions. Mesenchymal stem cell self-renewal and differentiation can be regulated by manipulating vitamin C, A, or D levels and by valine restriction.

CRediT

Author contributions: **Conceptualization -** Frederico Teixeira Izidorio, Márcia Cavalheiro Alves, Mateus Antunes Nogueira, Hugo Menezes Lopes; **Data**

curation - Frederico Teixeira Izidorio, Vittor Cândido Soares, Juliana da Silva Pereira, Marília de Andrade Salvá, Thamyres Veras Alves; **Formal Analysis-** Frederico Teixeira Izidorio, Márcia Cavalheiro Alves; **Investigation -** Frederico Teixeira Izidorio, Ricardo de Oliveira Carvalho; **Methodology -** Frederico Teixeira Izidorio; **Project administration -** Frederico Teixeira Izidorio; **Supervision-**Frederico Teixeira Izidorio; **Writing- original draft-** Frederico Teixeira Izidorio, Márcia Cavalheiro Alves, Mateus Antunes Nogueira, Ricardo de Oliveira Carvalho, Ana Claudia Santana Cano, Vittor Cândido Soares, Juliana da Silva Pereira, Marília de Andrade Salvá, Thamyres Veras Alves;
Writing-review & editing- Frederico Teixeira Izidorio, Márcia Cavalheiro Alves, Mateus Antunes Nogueira, Ricardo de Oliveira Carvalho, Ana Claudia Santana Cano, Vittor Cândido Soares, Juliana da Silva Pereira, Marília de Andrade Salvá, Thamyres Veras Alves.

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®.

Peer Review Process
It was performed.

References
1. Tipton KD. Nutritional Support for Exercise-Induced Injuries. Sports Med. 2015 Nov;45 Suppl 1:S93-104. doi: 10.1007/s40279-015-0398-4.
2. Kerksick CM, Arent S, Schoenfeld BJ, Stout JR, Campbell B, Wilborn CD, Taylor L, Kalman D, Smith-Ryan AE, Kreider RB, Willoughby D, Arciero PJ, VanDusseldorp TA, Ormsbee MJ, Wildman R, Greenwood M, Ziegenfuss TN, Aragon AA, Antonio J. International society of sports nutrition position stand: nutrient timing. J Int Soc Sports Nutr. 2017 Aug 29;14:33. doi: 10.1186/s12970-017-0189-4.
3. Cui P, Li M, Yu M, Liu Y, Ding Y, Liu W, Liu J. Advances in sports food: Sports nutrition, food manufacture, opportunities and challenges. Food Res Int. 2022 Jul;157:111258. doi: 10.1016/j.foodres.2022.111258.
4. Skorski S, Mujika I, Bosquet L, Meeusen R, Coutts AJ, Meyer T. The Temporal Relationship Between Exercise, Recovery Processes, and Changes in Performance. Int J Sports Physiol Perform. 2019; 14(8):1015-1021. doi:10.1123/ijspp.2018-0668.
5. Tobin MJ. Why Physiology Is Critical to the Practice of Medicine: A 40-year Personal Perspective. Clin Chest Med. 2019; 40(2):243-257. doi:10.1016/j.ccm.2019.02.012.
6. Foster C, Rodriguez-Marroyo JA, de Koning JJ. Monitoring Training Loads: The Past, the Present, and the Future. Int J Sports Physiol Perform. 2017;12(Suppl 2):S22-S28. doi:10.1123/ijspp.2016-0388.
7. Margaritelis NV, Paschalis V, Theodorou AA, Kyparos A, Nikolaidis MG. Redox basis of exercise physiology. Redox Biol. 2020; 35:101499. doi:10.1016/j.redox.2020.101499.
8. Ruegsegger GN, Booth FW. Health Benefits of Exercise. Cold Spring Harb Perspect Med. 2018 Jul 2;8(7). pii: a029694.
9. Cheng AJ, Yamada T, Rassier DE, Andersson DC, Westerblad H, Lanner JT. Reactive oxygen/nitrogen species and contractile function in skeletal muscle during fatigue and recovery. J Physiol. 2016 Sep 15;594(18):5149-60.
10. Yu X, Zuo Q. MicroRNAs in the regeneration of skeletal muscle. Front Biosci (Landmark Ed). 2013 Jan 1;18(2):608-15. doi: 10.2741/4124.
11. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993;75:843–54.
12. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281–97.
13. Bhuiyan SS, Kinoshita S, Wongwarangkana C, Asaduzzaman M, Asakawa S, Watabe S. Evolution of the myosin heavy chain gene MYH14 and its

intronic microRNA miR-499: muscle-specific miR-499 expression persists in the absence of the ancestral host gene. BMC Evol Biol 2013;13:142. doi:10.1186/1471-2148-13-142.

14. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009;136:215–33.
15. Ferraro, F. et al. Adult stem cells and their niches. Adv. Exp. Med. Biol. 2010, 695, 155–168.
16. Blanpain, C. et al. Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. 2004, Cell 118, 635–648.
17. Chacón-Martínez CA et al. Hair follicle stem cell cultures reveal self-organizing plasticity of stem cells and their progeny. EMBO J. 2017, 36, 151–164.
18. Rodríguez-Colman, M.J. et al. Interplay between metabolic identities in the intestinal crypt supports stem cell function. Nature, 2017, 543, 424.
19. Snoeck, H.W. Mitochondrial regulation of hematopoietic stem cells. Curr. Opin. Cell Biol. 2017, 49, 91–98.
20. Zheng, X. et al. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. Elife, 2016, 5, e13374.
21. Flores, A. et al. Lactate dehydrogenase activity drives hair follicle stem cell activation. Nat. Cell Biol. 2017, 19, 1017–1026
22. Rinschen MM. et al. Identification of bioactive metabolites using activity metabolomics. Nat. Rev. Mol. Cell Biol. 2019, 20, 353–367.
23. Agathocleous, M. et al. Ascorbate regulates haematopoietic stem cell function and leukaemogenesis. Nature, 2017, 549, 476–481.
24. Shapira SN, Christofk HR. Metabolic Regulation of Tissue Stem Cells. Trends Cell Biol. 2020 Jul;30(7):566-576. doi: 10.1016/j.tcb.2020.04.004.
25. Boisseau N, Barnich N, Koechlin-Ramonatxo C. The Nutrition-MicrobiotaPhysical Activity Triad: An Inspiring New Concept for Health and Sports Performance. Nutrients. 2022 Feb 22;14(5):924. doi: 10.3390/nu14050924.
26. BMJ (OPEN ACCESS) Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. doi: 10.1136/bmj.n160.
27. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj. 2017, 358: j4008, doi:10.1136/bmj.j4008
28. Balshem H et al. Grade guidelines: 3 ratng the quality of evidence. Journal of Clinical Epidemiology, Maryland Heights, 2011, v. 64, n. 4, p. 401-406.
29. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.
30. Torma F, Gombos Z, Jokai M, Berkes I, Takeda M, Mimura T, Radak Z, Gyori F. The roles of microRNA in redox metabolism and exercise-mediated adaptation. J Sport Health Sci. 2020 Sep;9(5):405-414. doi: 10.1016/j.jshs.2020.03.004.
31. Luo Z, Qi B, Sun Y, Chen Y, Lin J, Qin H, Wang N, Shi R, Shang X, Chen S, Chen J. Engineering Bioactive M2 Macrophage-Polarized, Anti-inflammatory, miRNA-Based Liposomes for Functional Muscle Repair: From Exosomal Mechanisms to Biomaterials. Small. 2022 Aug;18(34):e2201957. doi: 10.1002/smll.202201957.
32. Ding Z, Lin J, Sun Y, Cong S, Liu S, Zhang Y, Chen Q, Chen J. miR-122-5p negatively regulates the transforming growth factor-β/Smad signaling pathway in skeletal muscle myogenesis. Cell Biochem Funct. 2020 Mar;38(2):231-238. doi: 10.1002/cbf.3460.
33. Uhlemann M, Möbius-Winkler S, Fikenzer S, Adam J, Redlich M, Möhlenkamp S, Hilberg T, Schuler GC, Adams V. Circulating microRNA-126 increases after different forms of endurance exercise in healthy adults. Eur J Prev Cardiol. 2014 Apr;21(4):484-91. doi: 10.1177/2047487312467902.
34. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, Deans RJ, Keating A, Procko DJ, Horwitz EM. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy, 2006, v. 8, n. 4, p. 315-317.
35. Zuk PA, Zhu M, Ashjian P. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell; 2002, 13: 4279–4295.
36. Caplan AI, Buder SP. Mesenchymal stem cells: building blocks for molecular medicine in the 21st century. Trends Mol Med; 2001, 7: 259-64.

37. Thery C, Boussac M, Veron P, Ricciardi-Castagnoli P, Raposo G, Garin J, et al., Proteomic analysis of dendritic cell-derived exosomes: a secreted subcellular compartment distinct from apoptotic vesicles, J. Immunol. 2001, 166:7309–7318.
38. Baharlooi H, Nouraei Z, Azimi M, Moghadasi AN, Tavassolifar MJ, Moradi B, Sahraian MA, Izad M. Umbilical cord mesenchymal stem cells as well as their released exosomes suppress proliferation of activated PBMCs in multiple sclerosis. Scand J Immunol. 2020 Dec 18:e13013. doi: 10.1111/sji.13013.
39. Mears R, Craven RA, Hanrahan S, Totty N, Upton C, Young SL, et al., Proteomic analysis of melanoma-derived exosomes by two-dimensional polyacrylamide gel electrophoresis and mass spectrometry, Proteomics, 2004, 4:4019–4031, https://doi.org/10.1002/pmic.200400876.
40. R. Gastpar, M. Gehrmann, M.A. Bausero, A. Asea, C. Gross, J.A. Schroeder, et al., Heat shock protein 70 surface-positive tumor exosomes stimulate migratory and cytolytic activity of natural killer cells, Cancer Res. 2005, 65:5238–5247, https://doi.org/10.1158/0008-5472.can-04-3804.
41. W. Xu, Z. Yang, N. Lu, From pathogenesis to clinical application: insights into exosomes as transfer vectors in cancer, J. Exp. Clin. Cancer Res. 2016, 35: 156,https://doi.org/10.1186/s13046-016-0429-5.
42. H Valadi, K Ekstrom, A. Bossios, M. Sjostrand, JJ. Lee JO. Lotvall, Exosomemediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells, Nat. Cell Biol. 2007, 9:654–659, https://doi.org/10.1038/ncb1596.
43. B. Zhang, L. Shen, H. Shi, Z. Pan, L. Wu, Y. Yan, et al., Exosomes from Human Umbilical Cord Mesenchymal Stem Cells: Identification, Purification, and Biological Characteristics, 2016, p. 1929536, https://doi.org/10.1155/2016/1929536.
44. Zhuang G, Mao J, Yang G, Wang H. Influence of different incision designs on bone increment of guided bone regeneration (Bio-Gide collagen membrane +Bio-OSS bone powder) during the same period of maxillary anterior tooth implantation. Bioengineered. 2021 Dec;12(1):2155-2163. doi: 10.1080/21655979.2021.1932209. PMID: 34057023.
45. Mesimäki K, Lindroos B, Törnwall J, Mauno J, Lindqvist C, Kontio R, Miettinen S, Suuronen R: Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells. Int J Oral Maxillofac Surg 2009, **38**:201-209.
46. Stine RR. et al. PRDM16 maintains homeostasis of the intestinal epithelium by controlling region-specific metabolism. Cell Stem Cell, 2019, 25, 830–845.e8.
47. Sato T. et al. Single Lgr5 stem cells build crypt–villus structures in vitro without a mesenchymal niche. Nature. 2009, 459, 262–265.
48. Schell JC. et al. Control of intestinal stem cell function and proliferation by mitochondrial pyruvate metabolism. Nat. Cell Biol. 2017, 19, 1027–1036.
49. Cheng CW. et al. Ketone body signaling mediates intestinal stem cell homeostasis and adaptation to diet. Cell. 2019, 178, 1115–1131.e15.
50. Alonso S and Yilmaz ÖH. Nutritional regulation of intestinal stem cells. Annu. Rev. Nutr. 2018, 38, 273–301.
51. Fernandez-Barral A et al. Vitamin D differentially regulates colon stem cells in patient-derived normal and tumor organoids. FEBS J. 2019, 287, 53–72.
52. Beyaz S et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. Nature, 2016, 531, 53–58.
53. Mihaylova MM. et al. Fasting activates fatty acid oxidation to enhance intestinal stem cell function during homeostasis and aging. Cell Stem Cell, 2018, 22, 769–778.e4.
54. Ryall JG, Lynch GS. The molecular signature of muscle stem cells is driven by nutrient availability and innate cell metabolism. Curr. Opin. Clin. Nutr. Metab. Care, 2018, 21, 240–245.
55. Machado L. et al. In situ fixation redefines quiescence and early activation of skeletal muscle stem cells. Cell Rep. 2017, 21, 1982–1993.
56. Ryall JG. et al. The NAD+-dependent SIRT1 deacetylase translates a metabolic switch into regulatory epigenetics in skeletal muscle stem cells. Cell Stem Cell, 2015, 16, 171–183.