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

REVIEW ARTICLE

DOI: 10.54448/ijn23233

Tissue regeneration and gut microbiota-skeletal muscle axis via microRNAs and nutrition: a systematic review

Rodrigo Augusto Carvalho Junqueira[1*], Alexandre Carli Pinto[1]

[1] Dr. Rodrigo Junqueira Institute, Rio de Janeiro, Brazil.

*Corresponding Author: Dr. Rodrigo Augusto Carvalho Junqueira.
Instituto Dr. Rodrigo Junqueira, street: México, 41/Grupo 1307,
Rio de Janeiro, Brazil - CEP: 20031-905.
E-mail: racjunqueira@hotmail.com
DOI: https://doi.org/10.54448/ijn23233
Received: 05-02-2023; Revised: 07-05-2023; Accepted: 07-08-2023; Published: 07-10-2023; IJN-id: e23233

Abstract

Introduction: In the scenario of muscle regeneration in athletes, maintenance of skeletal muscle function is the prerequisite for tissue homeostasis and increased performance. MicroRNAs play a positive role in expanding our understanding of the controlling factors for skeletal muscle function. Recent progress has been made regarding gut microbiota, regenerative nutrition, and skeletal muscle metabolism. **Objective:** It was to carry out a systematic review of the main relations of regeneration of skeletal muscle-gut microbiota through nutrological functions, cells, and microRNAs. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from February to April 2023 in Scopus, PubMed, Science Direct, 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 217 articles were found. A total of 97 articles were fully evaluated and 49 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 54 studies at high risk of bias and 34 studies that did not meet the GRADE. It was concluded that miRNAs are widely present in skeletal muscle and play an irreplaceable tuning role in the proliferation, differentiation, apoptosis, development, and other physiological processes of skeletal muscle cells. The proposal that miRNAs are primarily involved in the cell's stress response makes miRNAs ideal for mediating the skeletal muscle response to changes in contractile activity. Research has accumulated evidence that confirms that miRNAs have played an important regulatory role in cell proliferation and differentiation, thus regulating skeletal muscle growth as highlighted in the small intestine by intestinal stem cells (LGR5+). The ketogenic or high-glucose diet regulates the self-renewal balance of LGR5+. Self-renewal and HSC differentiation can be regulated by manipulating vitamin C, A, or D levels and valine restriction. The composition of each athlete's microbiome influences sports performance.

Keywords: Muscle regeneration. Nutrition. Gut microbiota. microRNAs. Skeletal muscle. Performance. Athletes.

Introduction

In the scenario of muscle regeneration in athletes, the maintenance of skeletal muscle function is the prerequisite for tissue homeostasis and increased performance **[1,2]**. The body needs an effective way to regulate skeletal muscle growth, regeneration, and metabolism to make it in its best state **[3-5]**. In this sense, microRNAs play a positive role in expanding our understanding of the controlling factors for skeletal muscle function and improving the understanding and application of current therapeutic strategies in skeletal muscle diseases **[6,7]**.

Thus, several important findings were informed by studying athletes. Recent progress has been made regarding gut microbiota, regenerative nutrition, and skeletal muscle metabolism **[8-10]**. In this context, regular physical training associated with nutritional health has broad benefits for the health of the gut microbiota **[11-13]**.

In this context, physical exercise, nutrition, and gut microbiota are imperative in the process of muscle regeneration. In this context, mesenchymal stem cells (MSC) 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 **[14-16]**. The tissue niche is also able to influence MSC metabolism. Tissue stem cell metabolism has focused on central carbon metabolism, ie, the generation of metabolic building blocks via glycolysis, oxidative phosphorylation, or the pentose phosphate pathway. MSCs mediate tissue and organ homeostasis and regeneration by making decisions about whether to remain quiescent, proliferate, or differentiate into mature cell types. These decisions are directly integrated with the body's energy balance and nutritional status **[16]**.

In this sense, along with mesenchymal stem cells, microRNAs have emerged as critical regulators of numerous biological processes, modulating gene expression at the post-transcriptional level. The discovery of microRNAs as important new regulators of gene expression is expected to broaden our biological understanding of the regulatory mechanism in muscle, adding another regulatory dimension to the diversity and complexity of gene regulatory networks. Exercise-induced skeletal muscle injury and repair have always been at the forefront of sports medicine research. However, many mechanical problems that occur during regeneration and repair after skeletal muscle injury remain unresolved. It has become increasingly clear that regeneration of skeletal muscle development involves regulation by microRNAs. In recent years, the field has seen a rapid expansion of our knowledge of microRNAs in skeletal muscle regeneration. This study reviews microRNAs related to skeletal muscle regeneration and discusses the regulation of their expression in muscle and emerging issues of microRNA regulation **[17]**. Furthermore, therapeutic approaches point to crucial signaling pathways and molecules responsible for exercise-induced tissue regeneration, such as IGF1, PI3K, and microRNAs **[18]**.

Linked to this, specific GM responses induce the differentiation of a distinct set of RORγ+ regulatory T cells (Treg) crucial for intestinal homeostasis. The highly analogous populations of GM-dependent Treg cells promoted tissue regeneration in extra-intestinal sites, notably severely injured skeletal muscle, and fatty liver. Inflammatory mediators are induced by tissue damage combined with MHC class IIdependent T cell activation to drive the accumulation of gut-derived Treg RORγ+ cells in injured muscle, where they regulate the dynamics and content of early inflammation and help to balance inflammation. proliferation and differentiation of local stem cells **[19]**.

Given the above, the present study aimed to carry out a systematic review of the main relations of skeletal muscle regeneration-gut microbiota through nutrological functions, cells, and microRNAs.

Methods

Study Design

The systematic review rules of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis were followed. Available at: www.prismastatement.org/). Accessed on: 05/12/2023.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): *"Muscle regeneration. Nutrition. Gut microbiota. microRNAs. Skeletal muscle. Performance. Athletes"*. The research was carried out from February to April 2023 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Booleans "OR", "AND" and the operator "NOT" were used to target scientific articles of interest.

Study Quality and Risk of Bias

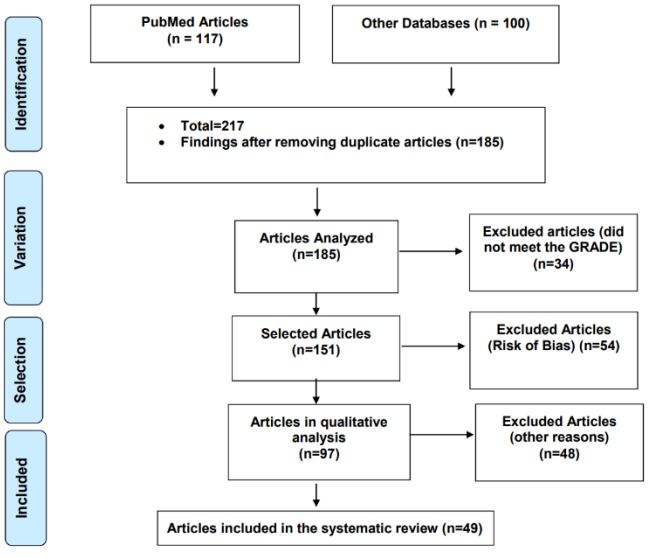
The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

Summary of Literary Findings

A total of 217 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the theme of this article, resulting in 151 articles. A total of 97 articles were evaluated in full and 49 were included and developed in this systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 54 studies with a high risk of bias and 34 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Major Findings – Muscle Regeneration and microRNAs

Metabolic homeostasis encompasses the interactions between diet, GM, and cellular enzymatic processes that generate the chemical pathways for perfect physiological and immunological functioning **[20-24]**. In this context, microRNAs have emerged as important actors in the regulation of gene expression, being involved in most of the biological processes examined so far. The proposal that miRNAs are primarily involved in the cell's stress response makes miRNAs ideal for mediating the skeletal muscle response to changes in contractile activity **[25,26]**.

In this respect, the skeletal muscle fiber, belonging to the terminally undifferentiated cell type, results mainly from the differentiation of myoblasts. Satellite cells in skeletal muscle are a kind of myoblasts in mature skeletal muscle tissue to form new muscle fibers or mix with previous muscle fibers to carry out skeletal muscle growth and development through proliferation and differentiation **[27,28]**.

Muscle growth and development processes are controlled by some transcription factors, including helix-loop-helix (HLH), myogenic regulatory factor (MRF), myogenic factor 5 (Myf5), MRF4, myocyte enhancing factor 2 (MEF2), and serum response factor (SRF) **[29,30]**. Research has accumulated evidence confirming that miRNAs have played an important regulatory role in cell proliferation and differentiation, thus regulating skeletal muscle growth **[31]**.

Thus, muscle-specific miR-1, miR-133, and miR-206 studies have gained great attention in exploring miRNA roles in myogenesis and increasing data from these researches may provide a comprehensive explanation for the mechanisms of myogenesis and the defined signal. cell proliferation and differentiation pathways **[29]**. Understanding the functions of miR-1 and miR-133 is the first significant step toward understanding the effects of miRNAs on the regulation of skeletal muscle growth and development. miR1's mechanism to promote muscle fiber differentiation may reduce HDAC4 expression and enhance MEF2 activity **[32]**.

Furthermore, miR-206 may also result in increased differentiation of myoblasts **[33]**. The gap junction protein connexin43 (Cx43) and Pola1 have been confirmed as the regulatory targets of miR-206 **[35]**. Cx43 must be involved in the initial stage of myogenesis. miR-206 reduces muscle fiber mutual contact by reducing Cx43 expression **[35]**. Adoption of miR-206 may lead to decreased Pola1 expression, which will reduce DNA synthesis in the early stage of differentiation and restrict cell proliferation during the period of myotube formation **[36]**. Unlike the functions of miR-1 and miR-206, miR133 can promote myoblast proliferation by suppressing SRF and restricting myoblast differentiation **[31,34]**. Another muscle-enriched miRNA is miR-486, which is highly induced during myoblast differentiation and exerts myogenic function **[37]**.

In addition, when miR-27b expression is contained and PAX3 expression remains at a certain level, cell proliferation will be promoted and differentiation will be delayed. During the transition period from cell proliferation to differentiation, some miRNAs are up-regulated while others are down-regulated **[38,39]**.

Gut microbiota, Nutrients and Muscle Performance

The practice of 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 **[18]**.

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 domain-containing proteins (JmjC), DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), ten-eleven DNA translocase demethylases (TETs), and histone deacetylases (HDACs). In this sense, metabolites can influence nutrient-sensing signaling pathways **[18,19]**.

Thus, the mechanistic target of the 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 detected within the cell. In addition, energy balance communicated via 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 kynurenine metabolite of tryptophan is an endogenous aryl hydrocarbon receptor agonist, and alpha-ketoglutarate (α-KG) binds to and activates IKKβ and initiates IKKβ signaling. NF-κβ **[21]**.

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+, 3hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2) is highly expressed while MPC1/2 is expressed at low levels. The ketogenic or high-glucose diet regulates the balance of autorenewal of LGR5+ HSC self-renewal and differentiation can be regulated by manipulation of vitamin C, A, or D levels and valine restriction **[20]**.

Concerning muscle regeneration, the nicotinamide riboside-rich diet may increase muscle stem cell numbers and function in a histone deacetylase (SIRT1) dependent manner **[40,41]**. Muscle stem cells, called satellite cells, are responsible for the maintenance of adult muscle mass and repair after injury. Several studies have demonstrated how changes in innate metabolism interfere with the differentiation of satellite stem cells into mature myocytes. For example, single-cell mapping with histone acetylation has shown that acetylation levels tend to be low in quiescent cells **[20,42]**.

The practice of 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 **[18]**.

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 domain-containing proteins (JmjC), DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), ten-eleven DNA translocase demethylases (TETs), and histone deacetylases (HDACs). In this sense, metabolites can influence nutrient-sensing signaling pathways **[18,19]**.

Thus, the mechanistic target of the 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 detected within the cell. In addition, energy balance communicated via 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 kynurenine metabolite of tryptophan is an endogenous aryl hydrocarbon receptor agonist, and alpha-ketoglutarate (α-KG) binds to and activates IKKβ and initiates IKKβ signaling. NF-κβ **[21]**.

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+, 3hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2) is highly expressed while MPC1/2 is expressed at low levels. The ketogenic or high-glucose diet regulates the balance of autorenewal of LGR5+ HSC self-renewal and differentiation can be regulated by manipulation of vitamin C, A, or D levels and valine restriction **[20]**.

Concerning muscle regeneration, the nicotinamide riboside-rich diet may increase muscle stem cell numbers and function in a histone deacetylase (SIRT1) dependent manner **[40,41]**. Muscle stem cells, called satellite cells, are responsible for the maintenance of adult muscle mass and repair after injury. Several studies have demonstrated how changes in innate metabolism interfere with the differentiation of satellite stem cells into mature myocytes. For example, single-cell mapping with histone acetylation has shown that acetylation levels tend to be low in quiescent cells **[20,42]**.

Conclusion

It was concluded that miRNAs are widely present in skeletal muscle and play an irreplaceable tuning role in the proliferation, differentiation, apoptosis, development, and other physiological processes of skeletal muscle cells. The proposal that miRNAs are primarily involved in the cell's stress response makes miRNAs ideal for mediating the skeletal muscle response to changes in contractile activity. Research has accumulated evidence that confirms that miRNAs have played an important regulatory role in cell proliferation and differentiation, thus regulating skeletal muscle growth as highlighted in the small intestine by intestinal stem cells (LGR5+). The ketogenic or high-glucose diet regulates the self-renewal balance of LGR5+. Self-renewal and HSC differentiation can be regulated by manipulating vitamin C, A, or D levels and valine restriction. The composition of each athlete's microbiome influences sports performance.

Acknowledgement

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@.

References
1. Liu C, Wu X, Vulugundam G, Gokulnath P, Li G, Xiao J. Exercise Promotes Tissue Regeneration: Mechanisms Involved and Therapeutic Scope. Sports Med Open. 2023 May 6;9(1):27. doi: 10.1186/s40798-023-00573-9.
2. Takemoto Y, Fukada SI. Molecular mechanism maintaining muscle satellite cells and the roles in sarcopenia. Clin. Calcium. 2017;27:339–344.
3. Bohnert KR, McMillan JD, Kumar A. Emerging Roles of ER Stress and Unfolded Protein Response Pathways in Skeletal Muscle Health and Disease. J. Cell. Physiol. 2017 doi: 10.1002/jcp.25852.
4. Bombieri F, Schena F, Pellegrini B, Barone P, Tinazzi M, Erro R. Walking on four limbs: A systematic review of Nordic Walking in Parkinson disease. Parkinsonism Relat. Disord. 2017;38:8–12. doi: 10.1016/j.parkreldis.2017.02.004.
5. Kasukawa Y, Miyakoshi N, Hongo M, Ishikawa Y, Kudo D, Suzuki M, Mizutani T, Kimura R, Ono Y, Shimada Y. Age-related changes in muscle strength and spinal kyphosis angles in an elderly Japanese population. Clin. Interv. Aging. 2017;12:413–420. doi: 10.2147/CIA.S113352.
6. Fan J, Kou X, Yang Y, Chen N. MicroRNA-Regulated Proinflammatory Cytokines in Sarcopenia. Mediat. Inflamm. 2016;2016:1438686. doi: 10.1155/2016/1438686.
7. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75:843–854.
8. 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.
9. 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.
10. 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.
11. 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.
12. Ruegsegger GN, Booth FW. Health Benefits of Exercise. Cold Spring Harb Perspect Med. 2018 Jul 2;8(7). pii: a029694.
13. 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.
14. Ferraro F. et al. Adult stem cells and their niches. Adv. Exp. Med. Biol. 2010, 695, 155–168.
15. Blanpain, C. et al. Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. Cell. 2004, 118, 635–648.
16. Chacón-Martínez CA et al. Hair follicle stem cell cultures reveal selforganizing plasticity of stem cells and their progeny. EMBO J. 2017, 36, 151–164.
17. 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.
18. Liu C, Wu X, Vulugundam G, Gokulnath P, Li G, Xiao J. Exercise Promotes Tissue Regeneration: Mechanisms Involved and Therapeutic Scope. Sports Med Open. 2023 May 6;9(1):27. doi: 10.1186/s40798-023-00573-9.
19. Hanna BS, Wang G, Galván-Peña S, Mann AO, Ramirez RN, Muñoz-Rojas AR, Smith K, Wan M, Benoist C, Mathis D. The gut microbiota promotes

distal tissue regeneration via RORγ+ regulatory T cell emissaries. Immunity. 2023 Apr 11;56(4):829-846.e8. doi: 10.1016/j.immuni.2023.01.033.

20. Rodríguez-Colman MJ. et al. Interplay between metabolic identities in the intestinal crypt supports stem cell function. Nature. 2017, 543, 424.
21. Snoeck HW. Mitochondrial regulation of hematopoietic stem cells. Curr. Opin. Cell Biol. 2017, 49, 91–98.
22. Zheng, X. et al. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. Elife, 2016, 5, e13374.
23. Flores A et al. Lactate dehydrogenase activity drives hair follicle stem cell activation. Nat. Cell Biol. 2017, 19, 1017–1026.
24. Rinschen MM. et al. Identification of bioactive metabolites using activity metabolomics. Nat. Rev. Mol. Cell Biol. 2019, 20, 353–367.
25. Kirby TJ, McCarthy JJ. MicroRNAs in skeletal muscle biology and exercise adaptation. Free Radic Biol Med. 2013 Sep;64:95-105. doi: 10.1016/j.freeradbiomed.2013.07.004.
26. Zhang S, Chen N. Regulatory Role of MicroRNAs in Muscle Atrophy during Exercise Intervention. Int J Mol Sci. 2018 Jan 30;19(2):405. doi: 10.3390/ijms19020405.
27. Buckingham M. Skeletal muscle formation in vertebrates. Curr. Opin. Genet. Dev. 2001;11:440–448. doi: 10.1016/S0959-437X(00)00215-X.
28. Nie M, Deng ZL, Liu J, Wang DZ. Noncoding RNAs, Emerging Regulators of Skeletal Muscle Development and Diseases. BioMed Res. Int. 2015;2015:676575. doi: 10.1155/2015/676575.
29. Ge Y, Chen J. MicroRNAs in skeletal myogenesis. Cell Cycle. 2011;10:441– 448. doi: 10.4161/cc.10.3.14710.
30. Potthoff MJ, Olson EN. MEF2: A central regulator of diverse developmental programs. Development. 2007;134:4131–4140. doi: 10.1242/dev.008367.
31. Harding RL, Velleman SG. MicroRNA regulation of myogenic satellite cell proliferation and differentiation. Mol. Cell. Biochem. 2016;412:181–195. doi: 10.1007/s11010-015-2625-6.
32. Sun Y, Ge Y, Drnevich J, Zhao Y, Band M, Chen J. Mammalian target of rapamycin regulates miRNA-1 and follistatin in skeletal myogenesis. J. Cell Biol. 2010;189:1157–1169. doi: 10.1083/jcb.200912093.
33. Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM, Conlon FL, Wang DZ. The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. Nat. Genet. 2006;38:228–233. doi: 10.1038/ng1725.
34. Anderson C, Catoe H, Werner R. MIR-206 regulates connexin43 expression during skeletal muscle development. Nucleic Acids Res. 2006;34:5863–5871. doi: 10.1093/nar/gkl743.
35. Cui Y, Xie S, Luan J, Zhou X, Han J. Quantitative proteomics and protein network analysis of A549 lung cancer cells affected by miR-206. Biosci. Trends. 2013;7:259–263. doi: 10.5582/bst.2013.v7.6.259.
36. Li RC, Tao J, Guo YB, Wu HD, Liu RF, Bai Y, Lv ZZ, Luo GZ, Li LL, Wang M., et al. In vivo suppression of microRNA-24 prevents the transition toward decompensated hypertrophy in aortic-constricted mice. Circ. Res. 2013;112:601–605. doi: 10.1161/CIRCRESAHA.112.300806.
37. Sun Q, Zhang Y, Yang G, Chen X, Zhang Y, Cao G, Wang J, Sun Y, Zhang P, Fan M, et al. Transforming growth factor-beta-regulated miR-24 promotes skeletal muscle differentiation. Nucleic Acids Res. 2008;36:2690–2699. doi: 10.1093/nar/gkn032.
38. Bakre A, Wu W, Hiscox J, Spann K, Teng MN, Tripp RA. Human respiratory syncytial virus non-structural protein NS1 modifies miR-24 expression via transforming growth factor-beta. J. Gen. Virol. 2015;96:3179–3191. doi: 10.1099/jgv.0.000261.
39. Crist CG, Montarras D, Pallafacchina G, Rocancourt D, Cumano A, Conway SJ, Buckingham M. Muscle stem cell behavior is modified by microRNA-27 regulation of Pax3 expression. Proc. Natl. Acad. Sci. USA. 2009;106:13383– 13387. doi: 10.1073/pnas.0900210106.
40. Antoniou A., Mastroyiannopoulos N.P., Uney J.B., Phylactou L.A. miR-186 inhibits muscle cell differentiation through myogenin regulation. J. Biol. Chem. 2014;289:3923–3935. doi: 10.1074/jbc.M113.507343.
41. Agathocleous, M. et al. Ascorbate regulates haematopoietic stem cell function and leukaemogenesis. Nature. 2017, 549, 476–481.
42. 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.
43. Stine RR. et al. PRDM16 maintains homeostasis

of the intestinal epithelium by controlling region-specific metabolism. Cell Stem Cell. 2019, 25, 830–845.e8.

44. Sato T. et al. Single Lgr5 stem cells build crypt–villus structures in vitro without a mesenchymal niche. Nature. 2009, 459, 262–265.

45. Bricker DK. et al. A mitochondrial pyruvate carrier required for pyruvate uptake in yeast, Drosophila, and humans. Science, 2012, 337, 96.

46. Herzig, S. et al. Identification and functional expression of the mitochondrial pyruvate carrier. Science. 2012, 337, 93.

47. Schell JC. et al. Control of intestinal stem cell function and proliferation by mitochondrial pyruvate metabolism. Nat. Cell Biol. 2017, 19, 1027–1036.

48. Cheng CW. et al. Ketone body signaling mediates intestinal stem cell homeostasis and adaptation to diet. Cell. 2019, 178, 1115–1131.e15.

49. Alonso S and Yilmaz ÖH. Nutritional regulation of intestinal stem cells. Annu. Rev. Nutr. 2018, 38, 273–301.