



Regenerative nutrition and gut microbiota signaling in skeletal muscle metabolism: a concise systematic review

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Abstract

Introduction: Recent progress has been made to gut microbiota, regenerative nutrition and skeletal muscle metabolism. In this context, regular physical training associated with nutrological health has broad benefits for the health of the intestinal microbiota. The triad physical exercise, nutrition and intestinal microbiota for the process of muscle regeneration, adult stem cells stand out as gut stem cells. **Objective:** the present study aimed to carry out a systematic review on the main cellular and molecular aspects of regenerative nutrition in the modulation of the intestinal microbiota and the metabolism of skeletal muscle. **Methods:** The rules of the Systematic Review-PRISMA Platform. The research was carried out from June 2021 to January 2022 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar. 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 215 studies were analyzed, with only 32 medium and high-quality studies selected, according to the rules of the GRADE, and with bias risks that do not compromise scientific development, based on the Cochrane instrument. A current focus in the field of sport and metabolism is the investigation of how specific metabolites and nutrients affect the progression and

treatment of muscle injuries. Nutrients can also regulate normal homeostatic processes, altering the decisions of muscle stem cells and satellites. Thus, the implications for understanding how diet influences cellular transitions are immense and will guide precision-based nutrition to improve overall health and therapeutic strategies for muscle injuries. Thus, metabolic pathways and chromatin modifications are closely linked, and hence 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.

Keywords: Regenerative Nutrition. Gut Microbiota. Metabolism. Skeletal Muscle.

Introduction

Many of the established positive health benefits of exercise have been documented by historic discoveries in the field of exercise physiology. These investigations generally assess performance thresholds or exercise-induced health benefits [1]. Thus, several important findings were informed by the study of athletes. Recent progress has been made to gut microbiota, regenerative nutrition and skeletal muscle metabolism [1-3].

In this context, regular physical training associated with nutrological health has broad benefits for the health of the intestinal microbiota, acting positively on almost

all organ systems of the body [4]. The mysteries of human physiology and the adaptive response to acute and chronic physical training have been largely elucidated through exercise science. Thus, exercise physiologists have studied the physiological response to physical activity and sports [5,6].

Also, the triad physical exercise, nutrition and intestinal microbiota for the process of muscle regeneration, adult stem cells (ASC) stand out as gut stem cells at the base (crypts) of the intestine and muscle stem cells outside the sarcolemma adjacent to the muscle basement membrane [7-9]. The tissue niche is also able to influence ASC metabolism. Tissue stem cell metabolism has focused on central carbon metabolism, that is, the generation of metabolic building blocks via glycolysis, oxidative phosphorylation, or the pentose phosphate pathway.

Besides, adult tissue stem cells mediate tissue and organ homeostasis and regeneration, 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. By-products and metabolic substrates that regulate epigenetic and signaling pathways are considered to have an instructive role, rather than an observer, in the regulation of cell fate decisions [9].

In this sense, it is suspected that the quiescent state of stem cells is characterized by an inherently glycolytic metabolism, followed by a transition to favor mitochondrial oxidative phosphorylation during differentiation [10-13]. However, growing 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 by signaling nutrients and the gut microbiota. In this scenario, metabolomics provides information on cellular pathways, observing substrates and metabolic products through different pathways [14,15]. Along with transcriptomics and proteomics analysis, it is observed that metabolism can affect cell fate (and vice versa) [16].

Therefore, the present study aimed to carry out a systematic review on the main cellular and molecular aspects of regenerative nutrition in the modulation of the intestinal microbiota and the metabolism of skeletal muscle.

Methods

Study Design

The rules of the Systematic Review-PRISMA

Platform (Transparent reporting of systematic reviews and meta-analysis-[HTTP://www.prisma-statement.org/](http://www.prisma-statement.org/)) were followed.

Data sources and research strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "Regenerative Nutrition. Gut Microbiota. Metabolism. Skeletal Muscle". The research was carried out from June 2021 to January 2022 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar. Also, a combination of the keywords with the booleans "OR", "AND", and the operator "NOT" were used to target the scientific articles of interest.

Study Quality and Bias Risk

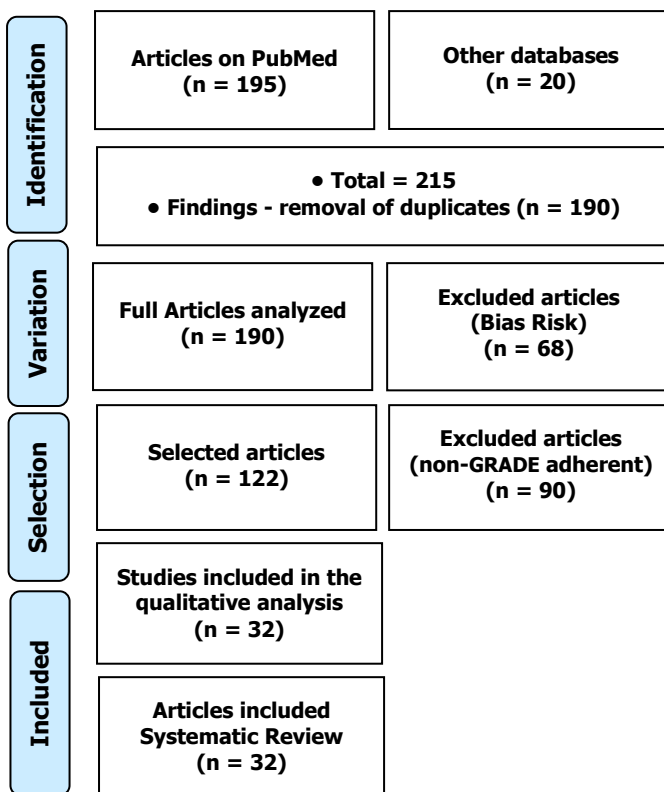
The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. Two independent reviewers carried out research and study selection. Data extraction was performed by reviewer 1 and fully reviewed by reviewer 2. A third investigator decided on some conflicting points and made the final decision to choose the articles.

Results and development

After the selectivity of articles and literary findings, a total of 215 studies were analyzed, with only 32 medium and high-quality studies selected, according to the rules of the GRADE, and with bias risks that do not compromise scientific development, based on the Cochrane instrument (Figure 1).

Nutrients, Gut Microbiota and Metabolism

Metabolism encompasses the interactions between diet, the microbiome, and the cellular enzymatic processes that generate the chemical pathways necessary to sustain life. The small intestine, comprising the duodenum, jejunum, and ileum, is the fastest self-renewal organ in men. 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 [17]. High rates of intestinal self-renewal are enabled by intestinal stem cells (LGR5+) at the base of intestinal crypts [18]. Cells in the gut can communicate via metabolic signals, with differentiated Paneth cells secreting lactate to support LGR5+ function [10].

Figure 1. Article selection (Systematic Review).

In this sense, the balance between LGR5+ and fate-differentiated cells can also be affected by cell-intrinsic changes in central carbon metabolism. The mitochondrial pyruvate carrier (MPC), comprising the subunits MPC1 and MPC2, is required for cross-species oxidation of pyruvate, allowing pyruvate to enter the mitochondria [18,19]. Genetic deletion of the MPC1 subunit or inhibition of MPC distorts cellular metabolism towards glycolysis and increases LGR5+ proliferation. On the other hand, overexpression of MPC1/MPC2 reduces the activity of LGR5+ [20].

A recent study demonstrated that the expression of the enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2), regulates the ratio-limiting step in ketone body synthesis, is enriched in LGR5+. Loss of Hmgcs2 impairs regeneration and promotes promiscuous differentiation to the Paneth cell line [21]. The ketone body β -hydroxybutyrate inhibits class I histone deacetylases to increase transcriptional activation of Notch signaling and maintain stem cell self-renewal [21].

Furthermore, the intestine is constantly finding nutrients derived from the diet and is therefore responsive to nutrient types [22]. For example, studies performed on patient-derived normal and tumor intestinal organoids have demonstrated that vitamin D levels can change the balance between stem cell fates

as well as their differentiation [23]. Therefore, LGR5+ activity, including proliferation and differentiation rates, is affected by large deviations in nutrient availability, as occurs in a high-fat diet or fasting [24-26].

Relationship Between Skeletal Muscle, Nutrients, And Regenerative Processes

Physical activity, endogenous metabolites, and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter the fate of the cell by controlling chromatin accessibility and downstream gene expression patterns [16].

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 DNA Translocase demethylases (TETs), and histone deacetylases (HDACs). In this sense, metabolites can influence nutrient detection signaling pathways [16].

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. Furthermore, the energy balance communicated through the cellular AMP/ADP-ATP ratio can be detected by AMP-activated protein kinase (AMPK). In addition, transcription factors can be directly regulated by metabolites, for example, the tryptophan kynurenine metabolite is an endogenous agonist of the aryl hydrocarbon receptor and alpha-ketoglutarate (α -KG) binds to and activates IKK β and initiates IKK β signaling. NF- κ B [16].

In this scenario, dietary manipulations and metabolites can 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. The ketogenic or glucose-rich

diet regulates the balance of self-renewal of LGR5+ Self-renewal and differentiation of HSC can be regulated by manipulating vitamin C, A, or D levels and by valine restriction [16].

Regarding muscle regeneration, a diet rich in nicotinamide riboside can increase muscle stem cell numbers and function in a histone deacetylase [enzyme 1 (sirtuin1, SIRT1)] dependent manner. Muscle stem cells, called satellite cells, are responsible for maintaining adult muscle mass and repairing it after injury. Several studies have demonstrated how changes in innate metabolism interfere with the differentiation of satellite stem cells into mature myocytes [27]. For example, mapping a single cell with histone acetylation showed that acetylation levels tend to be low in quiescent cells.

In this context, one 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 [28]. In this sense, SIRT1 is a target of increased glycolysis. SIRT1 represses the maturity expression of specific skeletal muscle genes as well as genes involved in mitochondrial biogenesis. Advanced glycolysis depletes NAD⁺, an essential metabolic cofactor of SIRT1, reducing SIRT1 activity and promoting downstream activation of these mature muscle-specific genes and differentiation [29].

Furthermore, transcription factors are directly regulated by metabolites [30,31]. 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 [32].

Thus, epigenetic signaling pathways and transcription are affected by changing nutrient levels. Furthermore, 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 [32]. Therefore, future research that defines the dietary and metabolic control of decisions about the fate of cells in muscle tissues will be of great importance in the fields of metabolism and regenerative medicine.

Conclusion

A current focus in the field of sport and metabolism is the investigation of how specific metabolites and nutrients affect the progression and treatment of muscle injuries. Nutrients can also regulate normal homeostatic processes, altering the decisions of muscle stem cells

and satellites. Thus, the implications for understanding how diet influences cellular transitions are immense and will guide precision-based nutrition to improve overall health and therapeutic strategies for muscle injuries. Thus, metabolic pathways and chromatin modifications are closely linked, and hence 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.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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