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REVIEW ARTICLE

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Investigation of regenerative nutrology of cells/molecules to the organism: a systematic review

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Abstract

Introduction: In the context of tissue regeneration and nutrology, stem cells from adult tissue mediate homeostasis and regeneration of tissues and organs. These decisions are directly integrated with the body's energy balance and nutritional status. Endogenous metabolites and dietary nutrients can directly influence epigenetic enzymes. **Objective:** It was to carry out a systematic review of the regenerative nutrology of cells and molecules in the body. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from April to June 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 112 articles were found. A total of 45 articles were evaluated in full and 25 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 18 studies that did not meet GRADE. It was evidenced that the metabolism of stem cells was centered on the central metabolism of carbon and the balance between glycolysis versus oxidative phosphorylation in the regulation of cell destiny. Epigenetic modifications to DNA and histones, proteins that alter cellular fate, control chromatin accessibility and downstream gene expression. In addition to the connection between metabolism and epigenetic pathways, nutrients can impact cellular status by modulating signaling pathway activity. A clear example is through the mechanistic targeting of the rapamycin (mTOR) signaling pathway, and in particular the mTOR 1 complex. Nutritional supplementation accelerated the healing of skin ulcers and reduced the intensity of wound care in non-malnourished patients.

Keywords: Nutrology. Tissue regeneration. Metabolism. Epigenetics. Nutrients.

Introduction

In the context of tissue regeneration and nutrology, adult tissue stem cells mediate 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 instructive, rather than bystander, roles in regulating cell fate decisions **[1]**.

In this sense, metabolism encompasses the interactions between the diet, the intestinal microbiota, and the cellular enzymatic processes that generate the chemical pathways necessary to maintain life. 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 **[2]**.

Furthermore, nutritional health acts directly on the human intestinal microbiota, impacting metabolism and the immune system for tissue regeneration. Scientific evidence is accumulating discoveries about the role of the "nutritional microbiota" in mechanisms involved in the regeneration of tissues, such as skin, liver, bone, and nervous system regeneration **[3]**.

Added to this, epigenetics also influences wound healing by targeting DNA, and key molecules such as RNA and microRNAs. Epigenetic factors also regulate transcription factors, cytokines, extracellular matrix proteins, and glycosaminoglycan. Nutrition is an epigenetic signal that can actively influence each step of the woundhealing process **[4]**. Wound healing requires dietary amino acids, vitamins, and minerals, although some natural compounds, including herbs and extracts, may have a synergistic effect to accelerate this process **[5]**.

Authors schematically reported essential nutrients for each stage of wound healing **[6]**. Adequate amounts of nutrients are necessary for the synthesis of nucleic acids (DNA and RNA), proteins, and other factors involved in tissue functional maturation and differentiation.8 Malnutrition is widely associated with delayed or failed healing, but nutritional intervention can mitigate malnutrition and improve wound healing, particularly by increasing collagen deposition after trauma **[7]**.

Given the above, the present study aimed to carry out a systematic review of the regenerative nutrition of cells and molecules in the body.

Methods

Study Design

The systematic review rules of the PRISMA Platform Available at: www.prismastatement.org/ were followed. Accessed on: 06/18/2023.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): *"Nutrology. Tissue regeneration. Metabolism. Epigenetics. Nutrients"*. The research was carried out from April to June 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Furthermore, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator was used to target scientific articles of interest.

Quality of Studies and Risk of Bias

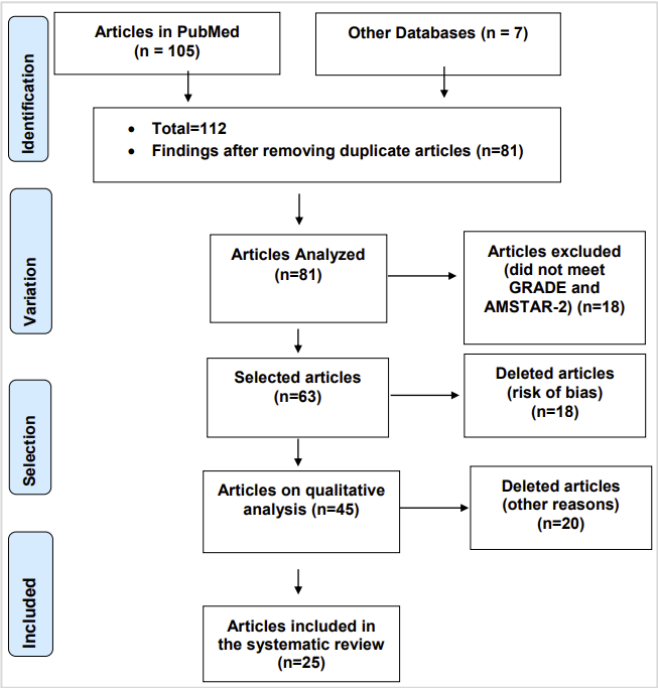
The quality of the studies was based on the GRADE instrument, prioritizing studies with scientifically rigorous methodology, randomized clinical studies, and clinical and/or pre-clinical studies with a significant sample size. The risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

Summary of Findings

A total of 112 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was carried out, removing articles that did not include the topic of this article, resulting in 81 articles. A total of 45 articles were evaluated in full and 25 were included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 18 studies that did not meet GRADE.

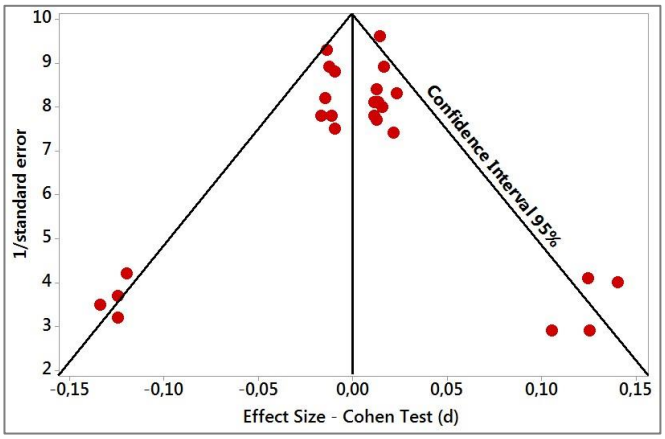
Figure 1. Flowchart showing the article selection process.



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 Magnitude of the difference (Effect size) using the Cohen Test (d). The sample size was determined indirectly by the inverse of the standard error. This graph presented symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the base of the graph and in studies with a large sample size that are presented in the upper region.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (NTotal= 25 studies evaluated in full in the systematic review).



Source: Own Authorship.

Metabolismo e Regeneração Nutrológica

Metabolism involves interactions between diet, intestinal microbiota, and cellular enzymes in the processes that generate the chemical pathways necessary to sustain life. Endogenous metabolites and nutrients derived mainly from the diet can directly influence epigenetic enzymes **[8]**. Epigenetic modifications to DNA and histones, proteins that alter cell fate, control chromatin accessibility and downstream gene expression **[9]**.

The majority of substrates and cofactors for chromatin-modifying enzymes are derived from metabolic pathways involving the tricarboxylic acid (TCA) cycle, the methionine cycle, the folate cycle, glycolysis, β-oxidation, and the hexosamine pathway **[10]**. These complex, interconnected networks generate intermediates that coactivate epigenetic enzymes and/or serve as direct substrates for modifications, including acetyl-CoA, alpha-ketoglutarate (α-KG), succinate, fumarate, S-adenosyl methionine (SAM), UDP-GlcNAc, ketone bodies, lactate and the reducing equivalents NADH and FADH2 **[11,12]**. Additionally, dietary-derived nutrients such as ascorbic acid (vitamin C) and sodium butyrate regulate the activity of chromatin and DNA-modifying proteins.

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact cellular state by modulating signaling pathway activity. A clear example is through the mechanistic target of rapamycin (mTOR) signaling pathway, and in particular mTOR complex 1 (mTORC1), which regulates cell growth only when nutrients and growth factors are present **[13]**.

In this regard, depletion of specific nutrients, such as arginine, leucine, and SAM, prevents growth factor-induced mTORC1 activation by blocking Rag GTPase-mediated recruitment of mTORC1 to the lysosome where it can be activated by Rheb GTPase **[14]**. Furthermore, nutrients impact the cellular state through AMP-activated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance, regulating cell growth and autophagy **[2]**.

In this scenario, most substrates and cofactors for chromatin-modifying enzymes are derived from metabolic pathways such as the tricarboxylic acid cycle, methionine cycle, folate cycle, glycolysis, β-oxidation, and hexosamine pathway. These complex, interconnected networks generate intermediates that coactivate epigenetic enzymes and/or serve as direct substrates for modifications, including acetyl-CoA, alpha-ketoglutarate (α-KG), succinate, fumarate, S-adenosyl methionine (SAM), UDP-GlcNAc, ketone bodies, lactate, NADH, FADH2 **[2]**.

In this context, ascorbic acid (vitamin C) and sodium butyrate regulate the activity of chromatin and DNA-modifying proteins. As the physiological concentrations of most chromatin substrates are in the range of the enzymatic Km constant values, the activity of epigenetic regulators is sensitive to the metabolic context, providing a direct link between metabolism and gene expression **[15]**. Table 1 presents the main functions of some vitamins, proteins, and minerals in the tissue regeneration and healing process **[15]**.

Table 1. The main functions of some vitamins, proteins, and minerals in the tissue regeneration and healing process.

✓ **In the inflammatory phase, vitamin A increases the release of cytokines;**
✓ **Bromelain and amino acids prevent prolonged inflammatory events;**
✓ **Vitamin C increases neutrophil migration and lymphocyte activation;**
✓ **In the proliferative phase, vitamin C is necessary for collagen synthesis;**

✓ **Glucosamine increases the production of hyaluronic acid;**
✓ **Vitamin A promotes the differentiation of epithelial cells;**
✓ **Zinc is necessary for DNA and protein synthesis and cell division;**
✓ **In the remodeling phase, amino acids and proteins play a key role in stabilizing the wound scar.**

Source: Own Authorship.

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact cellular state by modulating signaling pathway activity. For example, the mechanistic target of the rapamycin (mTOR) signaling pathway and, in particular, mTOR complex 1 (mTORC1), which regulates cell growth only when nutrients and growth factors are present. Depletion of specific nutrients including arginine, leucine, and S-adenosyl methionine prevents growth factor-induced mTORC1 activation by blocking Rag GTPase-mediated mTORC1 recruitment to the lysosome where it can be activated by Rheb GTPase **[2]**.

Another way that nutrients are sensed to impact cellular state is through AMP-activated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance, regulating cell growth and autophagy. Furthermore, transcription factors can be directly regulated by metabolites. Tryptophan kynurenine is an endogenous agonist for the aryl hydrocarbon receptor and alpha-ketoglutarate (α-KG) that binds and activates IKKβ and initiates NF-κβ signaling **[2]**.

In this regard, dietary manipulations and metabolites can affect tissue stem cells and direct cell fate decisions, as highlighted in the small intestine (intestinal stem cells), hematopoietic system, liver, and muscle (muscle stem cells/satellite stem cells). and hair follicle stem cells **[16]**. The self-renewal and differentiation of hematopoietic stem cells can be regulated by manipulating the levels of vitamin C, A, or D. Self-renewal of hematopoietic stem cells is also impaired by valine restriction A diet rich in methionine, which increases plasma homocysteine levels, impairs liver regeneration after partial hepatectomy **[2]**.

Furthermore, the intestinal epithelium is the fastest-renewing tissue and has great flexibility to adapt to different types of damage. Lgr5+ crypt-base cells act as stem cells during homeostasis and are essential during regeneration. Nutritional status and inflammation have recently been identified as regulators of stem cell activity in the human intestine **[17]**.

One study demonstrated that expression of the enzyme Hmgcs2, which regulates the ratio-limiting step in ketone body synthesis, is enriched in intestinal stem cells and LGR5+. Loss of Hmgcs2 impairs intestinal stem cell regeneration and promotes differentiation to the Paneth cell lineage. The ketone body β-hydroxybutyrate inhibits class I histone deacetylases to enhance transcriptional activation of Notch signaling and maintain stem cell self-renewal **[18]**.

Additionally, nutrients such as amino acids, polyunsaturated fatty acids, polyphenols, and vitamin D can improve skeletal muscle regeneration by targeting key functions of immune cells, muscle cells, or both **[19]**.

Signaling pathways including mTORC, AMPK, MAPK, and others are all sensitive to changes in nutrient levels. Furthermore, there are emerging examples of transcription factors being directly regulated by metabolites **[2,15]**. 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. The focus of the stem cell metabolism literature has centered on central carbon metabolism and the balance between glycolysis versus oxidative phosphorylation in regulating cell fate **[3]**.

Therefore, a multicenter, randomized, double-blind, and controlled study clinically investigated the potential of food enriched with high protein, arginine, and micronutrients, oral nutritional supplement (ONS), to improve pressure ulcer wound healing. Non-malnourished participants with category III or IV pressure ulcers were included. Patients were treated with 200mL of the specific ONS or a non-caloric control product three times daily, in addition to their regular diet and standard wound care, for a maximum of eight weeks. The results demonstrated that ONS supplementation accelerated pressure ulcer healing, indicated by a significantly faster decrease in ulcer size compared to control after eight weeks. The decrease in severity score (Pressure Ulcer Healing Scale) in the ONS group differed significantly from the control. Furthermore, blood vitamin C levels increased significantly in the ONS group compared to the control **[20]**.

Likewise, another randomized clinical study investigated the effectiveness of nutraceutical supplementation (arginine 9g, vitamin C 500mg, zinc 30mg) in healing pressure ulcers. A total of 17 patients with category II, III, or IV pressure ulcers were randomized to receive daily a standard hospital diet, a standard diet plus two high-protein/energy supplements, or a standard diet plus two high-protein/energy supplements. containing additional nutraceuticals. The results showed that only patients receiving supplementation with the additional nutraceutical demonstrated significant clinical improvement in pressure ulcer healing **[21]**.

Added to this, a study analyzed the effect of beta-hydroxybeta-methylbutyrate, arginine, and glutamine supplementation for four weeks on wound healing in 11 diabetic dialysis patients. After four weeks, according to the Bates-Jensen score, healing was observed in the wound depth score of seven (63.6%) patients and the wound appearance score of eight (72.7%) patients. While the wound depth score of four (36.4%) patients and the wound appearance score of three (27.3%) patients remained the same, no deterioration was observed in any of the cases during the entire follow-up period. This supplementation can positively contribute to wound healing in diabetic dialysis patients. The beneficial effects of arginine on wound healing are related to hormonal secretagogue actions mediated by arginine genes (growth hormone, prolactin, insulin and glucagon) **[22]**.

A randomized clinical study showed supplementation with antioxidant micronutrients and glutamine in accelerating wound healing. A total of 20 patients with wound-healing disorders were included. Patients received antioxidant micronutrients (ascorbic acid, alpha-tocopherol, beta-carotene, zinc, selenium) and glutamine (verum) or isoenergetic amounts of maltodextrin (placebo) for 14 days. The results showed that serum levels of micronutrients were not modified, except for selenium, which increased in the verum group (1.1±0.2 versus 1.4±0.2 µmol/l; p=0.009). Glutamine levels decreased only in the placebo group (562±68 versus 526±55 µmol/l; p=0.047). The prevalence of hypovitaminosis and VEGF-A concentration remained unchanged. Considering microcirculation, only oxygen saturation (O2) decreased in the placebo group. Wound closure occurred more quickly in the verum than in the placebo group **[23]**.

Finally, high-dose vitamin C supplementation helps in the healing process of surgical wounds in healthy individuals and those with pressure ulcers. Vitamin C supplementation in doses of 500mg, combined with at least 17mg of zinc, and even in combination with arginine, is useful for wound healing by increasing collagen synthesis **[60]**. Furthermore, vitamin C is essential for the formation of cross-links between collagen fibers, for the maturation of fibroblasts, and angiogenesis. Some studies have shown that patients with ulcers have deficient levels of vitamin C **[24,25]**.

Conclusion

It was concluded stem cell metabolism has focused on central carbon metabolism and the balance between glycolysis versus oxidative phosphorylation in regulating cell fate. Epigenetic modifications to DNA and histones, proteins that alter cell fate, control chromatin accessibility and downstream gene expression. In addition to the connection between metabolism and epigenetic pathways, nutrients can impact cellular state by modulating signaling pathway activity. A clear example is through the mechanistic target of the rapamycin (mTOR) signaling pathway, and in particular the mTOR complex 1. Nutrients impact cellular state through AMP-activated protein kinase (AMPK), which at low levels of ATP cell phosphorylates substrates to restore the cell's energy balance, regulating cell growth and autophagy. Nutritional supplementation accelerated the healing of skin ulcers and reduced the intensity of wound treatment in non-malnourished patients.

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Ethical Approval

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Informed consent

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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.

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