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Review Article

Role of Diet in Mesenchymal Stem Cells' Function: A Review

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ABSTRACT

Diet and lifestyle can greatly affect health and susceptibility to diseases. The nutritional needs of stem cells and their role in quantity and quality of stem cells is of great importance for cell renewal and healing process in injured tissues, because nutrients have an important role in stem cell physiology as many nutrient-derived metabolites released during the catabolic process can induce chromatin reshaping, epigenetic modifications and gene expression modulation. It seems that the maintenance of stem cell populations for tissue renewal and physiological restoration can be considered as one of hallmarks of health status. Based on the role of stem cell in tissue renewal and regeneration, establishing the nutrition requirements in diseases, during trauma recovery, and in aging process should come into consideration for establishing nutrient recommendations to decrease the prevalence of diseases and to advance the understanding of the biological pathways and mechanisms that connect stem cells nutrition requirements with diseases and aging.

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Introduction

Diet-related Diseases

Nutrition has been shown to be an accessible and potentially effective factor to improve global health and to decrease the rates of diet-related diseases. Diet can be a leading risk factor and cause of mortality for many diseases (1); including cardiovascular diseases, chronic renal failure, type II diabetes mellitus, inflammatory bowel disease IBD), etc. (2). In this context, aging has also been described as an independent risk factor for chronic diseases, including nutritional/environmental factors that can contribute to increased lifespan referred as "health span" (3). Regarding nutritional health span, in aging process, dysregulation of physiological systems and networks characteristics of chronic disease onset and progression happens (4), and can lead to a decrease in regenerative capacity of tissues via tissue remodeling, structure, and metabolism (5). Inflammation is another factor that can influence cellular senescence and a decline in cell number and function in various tissues (6).

Also in nutritional health span, the gut microbiota which has a vital role has been described (7).

Therefore; diet, aging, inflammation and microbiota have important role in maintaining health, tissue function and regenerative capacity of mesenchymal stem cells (MSCs) in various tissues; as the number of functional MSCs is modulated by interactions between genetic and epigenetic factors such as environmental exposures, and diet (8). MSCs are originated from stem cell niche that is the local environment of MSCs, while nutritional milieu was shown to impact their proper quantity and quality for further renewal and regeneration processes (9). So this review has focused on MSCs' function and their correlation with diet and nutritional milieu that can affect cell proliferation and differentiation.

Literature Selection and Screening

To describe relevant literature, a search strategy was developed to prepare data from PubMed, Web of Science, Scopus, and Scholar Google for this review. The search strategy included research journal articles, all published in English. Based on PRISMA principles (10). We obtained all literature mainly focusing on key words of diet, nutrition, function and mesenchymal stem cells. Only literature published from 2000 to 2023 were enrolled for review.

Stem Cells Definition

There are different types of stem cells including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and adult or MSCs (11). ESCs known as totipotent stem cells make up the early development of human embryo about four days after fertilization, and formation of blastocyst, and have the ability to divide into any type of mature and fully differentiated human cells. In blastocyst, the outer cells form the placenta and other accessory pregnancy tissues, while the inner cell mass called pluripotent stem cells can develop into any other cell type, but their disadvantage as tumorogenic potential has limited their use in regenerative medicine (12).

The iPSCs are embryonic-like and pluripotent that are generated from somatic cells that have been reprogrammed by the ectopic expression of defined embryonic transcription factors and are widely used in therapeutics for disease modeling, regenerative medicine, and drug discovery. They can be unlimited source of any type of human cell needed for therapeutic purposes in regenerative medicine, but the main concern and limitation in generation of iPSCs in regenerative medicine is their association with cancer (13).

Mesenchymal Stem Cells (MSCs)

MSCs divide mitotically, where one of its daughter cells remains a stem cell; yet the other one differentiates into a mature specialized cell and are not very numerous and only small numbers can be found in mature organs and tissues in stem cell niche (14). Since the discovery of MSCs as fibroblast-like cells within the bone marrow (BM) in 1966 (15), they have been isolated from other adult tissues including adipose tissue (16), endometrium (17), dental pulp (18), Wharton's jelly (19), and intestine (20); even bone-marrow-derived MSCs (BMSCs) are still considered a gold standard among MSCs in regenerative medicine (21).

Among MSCs, intestinal stem cells (ISCs) have a pivotal role in nutritional milieu. They are located at the crypts away from the intestinal content, whereas differentiated gut cells populate the villi, which directly contact the intestinal lumen. They are the cellular source of all mature cell types of the intestinal epithelium during adult life (22). ISCs in intestine are in adjacent to an array of functionally differentiated cells such as enterocytes, Paneth and goblet cells. These cells reside the intestinal epithelium and have a vital role in nutritional milieu. Paneth cells reside at the base of the intestinal crypts and lie in neighborhood to the ISCs, while their main function is to produce, package and export a variety of antimicrobial proteins and peptides including α-defensins, angiogenin-4, lysozyme and secretory phospholipase A2. Adjacent to them, goblet cells are present throughout the intestine and produce the protective mucus blanket by synthesizing and secreting high-molecular-weight glycoproteins known as mucins (23).

ISCs act as gut regenerative machinery that divide continually to replace their own population and to produce the differentiated epithelial subtypes. The nutritional status can affect production of enterocytes, secretory lineages such as Paneth cells and ISCs (24). Fasting and specific dietary exposures were demonstrated to decrease ISC population and function and the Paneth cells too (24). ISCs have been described to possess two populations named Lgr5+ and 4+ that are responsible for routine cell renewal and tissue regeneration, respectively. The 4+ ISCs are quiescent and can be mobilized in response to injury (25). An optimal food intake can regulate and activate ISCs' symmetric divisions (26).

Mesenchymal Stem Cells Characteristics

MSCs have unlimited proliferation capacity and multilineage differentiation properties (27). The International Society for Cell Therapy has described a minimal criteria for MSCs to be multipotent such as i) to be substrate/plastic adherent in cell culture plates (28); ii) to possess specific phenotype with positive expression of some markers as CD73,

CD90, and CD105, and at the same time negative expression of some markers as CD11b, CD14, CD34, CD45, CD79a, and human leucocyte antigen DR HLA-DR) (29); iii) and the ability to differentiate into adipocytes, chondrocytes, and osteocytes (30).

Their ability to differentiate into one or more types of mature cells is called "developmental plasticity", and various stem cells have different degrees of potency. They can be easily isolated and expanded *in vitro*, and have low immunogenicity making them an ideal candidate for cell transplantation in the field of regenerative medicine (31). MSCs can support tissue regeneration under both physiologic and pathologic conditions. They participate in tissue homeostasis, in a dynamic and specialized microenvironment with a distinct design as stem cells niche. These cells are immune-modulating because of the low expression of CD40, CD80, CD86, major histocompatibility complex I MHC I), and the lack of MHC II expression (32).

Their immune-modulating function is via interacting with immune cells such as dendritic cells DCs), T and B cells, neutrophils, natural killer cells NKs), and macrophages as well as powerful paracrine actions (33). They can be easily labeled and tracked by non-invasive methods such as MRI and can be a drug carrier (34). MSCs have been used in tissue engineering too (35). They have an active component of paracrine secretion as exosomes or extracellular vesicles (EVs) that have been utilized in treatment of many diseases (36). Exosomes can cross the blood-brain barrier BBB) to enter the CNS and to be employed in treatment of brain diseases (37). MSCs naturally package MicroRNAs (miRNAs) into exosomes and can be potentially employed to package exogenous therapeutic miRNAs; while miRNAs are non-coding RNAs that play an important role in gene regulation (38).

Mesenchymal Stem Cells and Health

MSCs were shown to have an important role in maintaining health and tissue function throughout the lifespan based on their regenerative capacity in various tissues (39). They have multi-differentiative potential to create the needed cell types for replacement of all cells that comprise the organ where they reside, their dynamic balance for cell proliferation, self-renewal, and differentiation to provide the immediate needs for tissue growth and function, and repair throughout the lifespan has a vital role (40). The number of functional MSCs was shown to be modulated by interactions between genetic and epigenetic factors including environmental exposures, and diet exercise (41). So the nutritional needs of stem cells for cell renewal and healing process in injured tissues and the role of a diet in quantity and quality of stem cells is of great importance (42), even aging can lead to a depletion of MSC populations referred to stem cell exhaustion that can limit the ability of stem cells to replenish injured tissues and to maintain essential physiological functions via a decline in the capacity of cell self-renewal and differentiation (43).

MSCs in proper quantity and quality have been successfully utilized in treatment of several acute and chronic diseases for structural and functional restoration of injured tissues (44). Their function and plasticity were illustrated to be closely associated with inflammation (45) by secretion of inflammatory cytokines such as IL-1, IL-6, and TNF-α (46), and in response to bacterial lipopolysaccharides (LPS) (46). In pathophysiological conditions such as obesity, their proliferation and differentiation are impacted by pro-inflammatory cytokines (47) and contribute to obesity-associated inflammation and metabolic disorders (48). They are also involved in pathogenesis, development, progression and metastasis of cancer through the secretion of cytokines and chemokines (49).

Mesenchymal Stem Cells and Nutrition

Diet and lifestyle are important factors to affect health and susceptibility to diseases. They impact the quantity and quality of available stem cells in the stem cell niche for renewal, regeneration and physiological restoration as hallmarks of health (9). Deficits in the nutritional milieu can alter stem cell niche and/or the interaction of stem cells with the niche and lead to age-related modifications for stem cell proliferation and function. As stem cells have unique metabolism, their nutrient needs and in differentiated cells are of great importance. Therefore, understanding the nutritional needs of stem cells during life span, including the role of nutrition in extending biological age by blunting biological systems decay is fundamental to establish food and nutrient guidance to decrease prevalence of diseases and to maintain the overall health (9).

MSCs as the progenitors for tissues were illustrated to be highly pertinent for childhood obesity and metabolic disease risk of adipose and skeletal muscle (50). In this context, nutrients may directly or indirectly affect stem cells by regulating the stem cell niche non-autonomously. Nutrients also regulate hormone production, which in turn can impact the stem cell behavior and their niche. In response to these stimuli, stem cells activate signaling pathways, reprogram their metabolism and gene expression, and convert the dietary input into fate decisions. Stem cell characteristics that are regulated by nutrients are balanced symmetric/

asymmetric divisions, gene expression, genome and epigenome integrity, autophagy, metabolism, oxidative status, self-renewal, differentiation, and exhaustion. Stem cells adapt their proliferation to nutrients and available growth factors in order to conduct cell division when there are enough nutrients. Mechanistically, this tight balance is dependent on "master regulators", such as mTORC1, which can sense nutrients and regulate both metabolism and stem cell fate (51).

On the other hand, intracellular metabolites, such as acetyl-CoA can regulate both metabolic pathways and epigenetic processes, and then connecting diet and metabolism with stem cell functions (52). This connection is specifically relevant in fate determination for various stem cells, while stem cell self-renewal can be achieved by modifying calories or nutrients (53). So stem cells are among the main players in orchestrating the response of the body to nutrients, mainly due to their key role in tissue homeostasis and contribution to health maintenance (54), because stem cells not only use nutrients for their metabolic needs; but also adapt their functions, such as self-renewal, autophagy, or differentiation. It seems that the metabolic environment, nutrient availability and diet-induced metabolic alterations affect stem cell fate, lineage specification and differentiation (55).

In this relation, nutrients are important in stem cell physiology due to the ability of several nutrient-derived metabolites released during the catabolic process to induce chromatin reshaping, epigenetic modifications and gene expression modulation (56), and the molecular pathways responsible for sensing nutrient availability control key functions of protein synthesis, self-renewal, autophagy, and differentiation (57). The influence of diet on stem cells can become more dramatic because stem cells have unique metabolic needs which change based on the developmental stage of stem cells (58). The activation of metabolic pathways is necessary for specific activities of stem cells, producing more profound nutrient dependencies in comparison to differentiated cells (59). Stem cells when compared to differentiated cells had lower levels of reactive oxygen species (ROS); while ROS accumulation and the total intracellular oxidation state were greatly impacted by diet and nutrients. They were considered pivotal regulators of the balance between self-renewal and differentiation (60).

Mesenchymal Stem Cells and Amino Acids

Amino acids (AAs) are involved in self-renewal, maintenance of pluripotency and differentiation ability of stem cells (61). Several essential AAs (EAAs) have been mentioned to be necessary for the maintenance of MSCs (62); and their abundance was exhibited to increase proliferation, without affecting the stemness (63). It was shown that MSCs significantly increased after receiving essential amino acids (EAA's) versus placebo at 24-h. It was shown that the Mammalian Target of Rapamycin Complex 1 (mTORC1) is a primary nutrient sensor in the intestine acting as an important regulator of protein synthesis and growth, affecting stem cell proliferation and autophagy in the intestine (64).

Restriction of dietary protein and amino acids has been shown to affect stem cell fate. E.g. methionine deficiency can decrease proliferation of ISCs (65). In Drosophila, the depletion in EAA's, methionine, and the methionine derived S-adenosyl methionine was found to decrease midgut mitosis in ISCs by controlling protein synthesis and by induction of the Jak/STAT ligand Unpaired 3 (Upd3) (66). Induction of the JNK pathway increases in ISCs differentiation, whereas ISC proliferation remain unchanged, despite the downregulation of Jak/STAT pathway (67). So methionine was exhibited to act as a regulator of cell proliferation (68).

The role of leucine to promote myoblast proliferation and differentiation through an mTORC1-MyoD cascade has been described (69). The mTOR has a key role in diverse cellular processes including cell growth, differentiation, and protein synthesis through its role in regulating the expression of specific genes (70). Arginine was reported to have a critical role in proliferation and renewal of ISCs and tissue regeneration (71). Glutamine apart from glucose has been the second most consumed nutrient during the proliferation phase of myoblasts (72), suggesting their important role in cell proliferation (73). Diet supplementation with conditionally EAA's glutamine resulted in activation of ISCs, including a rise in total intestinal cell number (74). Dietary glutamate stimulate ISC proliferation and growth through calcium signaling (75).

Mesenchymal Stem Cells and Fatty Acids

Fatty acids (FAs) are another group of nutrient-derived molecules that are important for stem cell physiology confirmed by presence of a specific lipidome signature in MSCs, playing a primary role in quiescence and self-renewal, symmetric-asymmetric division, differentiation, cell-niche interaction and cell fate determination of MSCs (76). High-fat diet (HFD) can induce alterations in intestinal structure and function (77), via changes in control of ISC activity. It was shown that specific fatty acids, including palmitic acid and oleic acid, directly interact with the ISCs and induce

peroxisome proliferator-activated receptor delta (PPAR-δ) specifically in ISCs and progenitor cells to enhance their stemness (78).

It is necessary to mention that in stem cells, a well-balanced combination of FA synthesis (FAS) and FA oxidation (FAO) is indispensable, and inhibition of one or the other can result in stem cell exhaustion (76). High-fat diets increase ISC proliferation, and self-renewal, while decreasing Paneth cell number and lead to a rise in the risk of intestinal hyperplasia (64). In mice fed a high fat western-style diet, it was shown that transcriptional reprogramming happens in both Lgr5+ and 4+ ISCs populations, with stem cell mutation and nutrient-driven alterations in stem cell populations that are in consistent with a carcinogenesis event (79). Mechanistically, HFD-induced stress leads to JNK pathway activation, secretion of Upd3 ligand and activation of ISC proliferation through the Jak/STAT signaling pathway (80).

In Drosophila, microbiota-derived short chain fatty acids (SCFAs) were demonstrated to regulate lipid and carbohydrate metabolism to maintain ISCs (81). Epithelial injury causing exposure of crypt ISCs to butyrate suppresses ISC proliferation and mucosal wound healing via Foxo3 regulation. In Drosophila, high cholesterol diets were presented to alter ISC cell differentiation by modulating the Delta ligand and Notch stability in the endoplasmic reticulum (77). An association between MSCs fat content with adiposity and metabolic health was prospectively shown. Fetal MSCs were demonstrated to be progenitors for mesodermal tissues, including adipose and skeletal muscle and these MSCs when exposed to obesity in utero were illustrated to have more *in vitro* potential for adipogenic differentiation and higher fat content. The fat content of MSCs undergoing adipogenesis *in vivo* was also reported to have positive correlation with neonatal adiposity (50).

Mesenchymal Stem Cells and Phytochemicals

Another group of nutrients that have a vital role in stem cell physiology are phytochemicals for their beneficial impact on human health based on their fundamental roles in cell signaling, cell cycle regulation, oxidative stress response, inflammation, and many other processes (82). Among phytochemicals, polyphenols were illustrated to modulate the behavior of stem cells, either directly or indirectly, by regulating the microenvironmental niche, suppressing hydrogen peroxide-induced oxidative stress (83) and inducing osteogenic differentiation (84).

Vitamin A derived from carotenoids as the most important phytochemical is a potent genetic and epigenetic modulator of stem cell self-renewal and differentiation (85). It participates in hematopoiesis (86), and contribute in dormancy of hematopoietic stem cell (87). It can modulate antioxidant and anti-inflammatory pathways by regulating key effectors, such as SIRT1, Wnt, NF-kappa B and Nrf2 (88). Biotin (Vitamin B7) sodium multivitamin transporter (Smvt) was shown to be specifically expressed in ISCs, highlighting the metabolic requirements of ISCs for this vitamin (89). In a recent study, biotin transported to the ISCs via Smvt was found to be necessary for mitosis and physiological intestinal cell differentiation, in a process parallel to the Jak/STAT pathway. Furthermore, ISC-specific Smvt silencing leads to dysbiosis caused by increased load of the opportunistic pathogen Providencia sneebia. Strikingly, in biotin-scarce conditions, microbiota-produced biotin could directly induce ISC mitosis (90).

Mesenchymal Stem Cells and Minerals

Early-life abnormal dietary calcium intake might program the adipogenic differentiation ability of MSCs from male offspring, with significant expressions on the Wnt/β-catenin signaling pathway to aggravate high-fat-diet-induced obesity in adulthood (91). This adipogenic differentiation can be regulated by coordination of complex networks in several signaling pathways, including JAK2/STAT3, SIRT1/SIRT2, ERK1/ERK2, TGF-β/BMP, Wnt/β-catenin and RHO-family GTPase (92), while activation of Wnt/β-catenin signaling can further inhibit adipogenic differentiation and promote osteogenic differentiation through endogenous regulatory genes such as CTNNB1, Wnt1, Wnt10a, Wnt10b, Wnt5a, Gsk3β, Axin2 and TGF7L2 (93). This differentiation potential was significantly declined with the age (93), so the nutritional status and exposure to adverse factors during pregnancy and lactation have important role in differentiation potential of MSCs to affect later metabolic disturbances in adulthood (94). The Ca2+ formed in the culture medium was shown to have osteo-inductive properties to promote osteogenic differentiation of MSCs (95).

Mesenchymal Stem Cells and Energy

It was reported that alterations in energy sources through glycolysis, the tricarboxylic acid cycle, in addition to accompanying changes in ROS generation can impact stem cell differentiation (96). ISCs were demonstrated to have robust responses to energy intake including caloric restriction, fasting and various energy sources derived from ketogenic, high-fat, or high-carbohydrate diets (25). In this context, energy has been described as the

Lkb1/AMPK activated kinase pathway to act as a metabolic checkpoint and master regulator of stem cell proliferation and fate. This pathway is activated when ATP is decreased and cell growth is terminated leading to suppression of mTORC1 signaling. So the complex relationship between mTORC1 and LKB1-AMPK activity can impact on SC proliferation, apoptosis, and self-renewal (64), because LKB1-AMPK signaling affect Sirt1 and is stimulated by caloric restriction, fasting, and exercise, that can simulate the expansion of the intestinal stem cells and increase the capacity for tissue repair and regeneration (97).

Sirt1 by impacting nicotinamide adenine dinucleotide+ (NAD+) acts as a NAD-dependent histone and nonhistone protein deacetylase and regulates gene expression, and cell proliferation, metabolism, and differentiation. As Sirt1 level decreases with age and rescued by dietary NAD, it can influence the SC quantity (98). Ketogenic diets mimic low-caloric states via enhancing stem cell self-renewal and tissue regeneration and dampening the progressive loss of tissue function during aging; while diets with high carbohydrate levels have opposing effects (99). The intracrine ketone bodies can define the fate for intestinal stem cells and play the role as mediators of the pro-regenerative effects of fasting. High-carbohydrate diets were shown to suppress formation of ketone bodies and impair function, self-renewal, stemness, regenerative capacity and epithelial homoeostasis of ISCs via promoting formation of Paneth and goblet cells at the expense of formation of enterocytes (99).

ISCs sense and respond differently to dietary energy sources and macronutrients. Ketogenic diets can improve intestinal health as the increased generation of ketone bodies impact Lgr5+ stem cells function and intestinal epithelial homeostasis. Inhibition in formation of ketone bodies in Lgr5+ cells can weaken stemness by enhancing formation of goblet and Paneth cells. It is now known that release of Wnt ligands and stem cell growth factors by Paneth cells can protect epithelial homeostasis (99). Dietary supplementation with N-acetyl-D-glucosamine (GlcNAc) was reported to be enough to maintain ISC proliferation during caloric restriction independent of food intake (98). High-sugar diets can induce alterations in intestinal structure and function and ISCs (82), via changes in control of ISC activity.

Mesenchymal Stem Cells and Microbiota

In nutritional health span, the gut microbiota was demonstrated to have a vital role (7). A complex interplay has been displayed between microbiota, diet and the intestine controlling host health and the stem cell niche. The microbiota affects directly on intestinal activity and their stem cell niche through its contribution to energy harvest and storage, and micronutrient synthesis, including vitamins that the host body cannot produce, enhance fermentation-mediated digestive efficiency and absorb undigested nutrients. It was shown that gut microbiota stimulates ISCs function and participates in homeostasis maintenance of stem cells (23). ISCs have a pivotal role in epithelial renewal and turnover, proliferation to maintain a steady stem cell population and differentiation to produce functional epithelial cell types. This happens in an elaborate micro-environment via a myriad of host and gut microbiota-derived signals, forming an intestinal stem cell niche (100).

Conclusion

Diet and lifestyle can greatly affect health and susceptibility to diseases. The nutritional needs of stem cells and their role in quantity and quality of stem cells is of great importance for cell renewal and healing process in injured tissues, because nutrients have an important role in stem cell physiology as many nutrient-derived metabolites released during the catabolic process can induce chromatin reshaping, epigenetic modifications and gene expression modulation. It seems that the maintenance of stem cell populations for tissue renewal and physiological restoration can be considered as one of hallmarks of health status. Based on the role of stem cell in tissue renewal and regeneration, establishing the nutrition requirements in diseases, during trauma recovery, and in aging process should come into consideration for establishing nutrient recommendations to decrease the prevalence of diseases and to advance the understanding of the biological pathways and mechanisms that connect stem cells nutrition requirements with diseases and aging.

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Conflict of Interest

None declared.

References

1 Janssen F, Bardoutsos A, Vidra N. Obesity prevalence in the long-term future in 18 European countries and in the USA. *Obes Facts*. 2020;13:514-27. DOI: 10.1159/000511023. PMID: 33075798.

2 Mehrabani D, Vahedi M, Eftekhari MH, et al. Food Avoidance in Patients with Ulcerative

Colitis: A Review. *Int J Nutr Sci*. 2017;24:189-195.
3 Baghdadi M, Hinterding HM, Partridge L, et al. From mutation to mechanism: deciphering the molecular function of genetic variants linked to human ageing. *Brief Funct Genomics*. 2022;21:13-23. DOI: 10.1093/bfgp/elab005. PMID: 33690799.
4 Tierney MT, Stec MJ, Rulands S, et al. Muscle stem cells exhibit distinct clonal dynamics in response to tissue repair and homeostatic aging. *Cell Stem Cell*. 2018;22:119-27e3. DOI: 10.1016/j.stem.2017.11.009. PMID: 29249462.
5 Gheller BJ, Riddle ES, Lem MR, et al. Understanding age-related changes in skeletal muscle metabolism: differences between females and males. *Annu Rev Nutr.* 2016;36:129-56. DOI: 10.1146/annurev-nutr-071715-050901. PMID: 27431365.
6 Homayoun M, Mehrabani D, Edalatmanesh MA, et al. The Role of Lithium Chloride in Nutrition and Stem Cell Growth Kinetics: A Review. *Int J Nutr Sci*. 2021;6:6-13. DOI: 10.30476/IJNS.2021.88801.1104.
7 Treveil A, Sudhakar P, Matthews ZJ, et al. Regulatory network analysis of Paneth cell and goblet cell enriched gut organoids using transcriptomics approaches. *Mol Omics*. 2020;16:39-58. DOI: 10.1039/c9mo00130a. PMID: 31819932.
8 Nugent R, Bertram MY, Jan S, et al. Investing in non-communicable disease prevention and management to advance the sustainable development goals. *Lancet.* 2018;391:2029-35. DOI: 10.1016/S0140-6736(18)30667-6. PMID: 29627167.
9 Stover PJ, Field MS, Brawley HN, et al. Nutrition and stem cell integrity in aging. *J Intern Med.* 2022;29:587-603. DOI: 10.1111/joim.13507. PMID: 35633146.
10 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535b2535. DOI: 10.1136/bmj.b2535. PMID:19622551.
11 Mehrabani D, Rabiee M, Tamadon A, et al. The growth kinetic, differentiation properties, karyotyping, and characterization of adipose tissue-derived stem cells in hamster. *Comp Clin Pathol.* 2016;25:1017-22. DOI:10.1007/s00580-016-2300-7.
12 Hosseini-Asl SK, Mehrabani D, Karimi-Busheri F. Therapeutic Effect of Mesenchymal Stem Cells in Ulcerative Colitis: A Review on Achievements and Challenges. *J Clin Med.* 2020 Dec 3;9:3922. DOI: 10.3390/jcm9123922. PMID: 33287220.
13 Kaboodkhani R, Mehrabani D, Karimi-Busheri F. Achievements and Challenges in Transplantation of Mesenchymal Stem Cells in Otorhinolaryngology. *J Clin Med.* 2021;10:2940. DOI: 10.3390/jcm10132940. PMID: 34209041.
14 Aliborzi G, Vahdati A, Mehrabani D, et al. Isolation, Characterization and Growth Kinetic Comparison of Bone Marrow and Adipose Tissue Mesenchymal Stem Cells of Guinea Pig. *Int J Stem Cells*. 2016;9:115-23. DOI: 10.15283/ijsc.2016.9.1.115. PMID: 27426093.
15 Aliborzi G, Vahdati A, Hossini SE, et al. Evaluation of bone marrow-derived mesenchymal stem cells for regeneration from Guinea pigs. *OL J Vet Res.* 2015;19:450-9.
16 Kamali-Sarvestani A, Hoseini SE, Mehrabani D, et al. Effects in rats of adolescent exposure to Cannabis sativa on emotional behavior and adipose tissue. *Bratisl Med J.* 2020;12:297-301. DOI: 10.4149/BLL_2020_047. PMID: 32356446.
17 Ghobadi F, Rahmanifar F, Mehrabani D, et al. Endometrial mesenchymal stem stromal cells in mature and immature sheep: An in vitro study. *Int J Reprod Biomed*. 2018;16:83-92. DOI: 10.29252/ijrm.16.2.83.3. PMID: 29675492.
18 Zare S, Mehrabani D, Jalli R, et al. MRI-Tracking of Dental Pulp Stem Cells In Vitro and In Vivo Using Dextran-Coated Superparamagnetic Iron Oxide Nanoparticles. *J Clin Med*. 2019;89:1418. DOI: 10.3390/jcm8091418. PMID: 31505807.
19 Nazempour M, Mehrabani D, Mehdinavaz-Aghdam R, et al. The effect of allogenic human Wharton's jelly stem cells seeded onto acellular dermal matrix in healing of rat burn wounds. *J Cosmet Dermatol*. 2020;19:995-1001. DOI: 10.1111/jocd.13109. PMID: 31556227.
20 Mani KK, El-Hakim Y, Branyan TE, et al. Intestinal epithelial stem cell transplants as a novel therapy for cerebrovascular stroke. *Brain Behav Immun*. 2023:10:345-60. DOI:10.1016/j.bbi.2022.10.015. PMID: 36328163.
21 Khodabandeh Z, Mehrabani D, Dehghani F, et al. Spinal cord injury repair using mesenchymal stem cells derived from bone marrow in mice: A stereological study. *Acta Histochem*. 2021;123:151720. DOI: 10.1016/j.acthis.2021.151720. PMID: 34083065.
22 Barker N, Van Es JH, Kuipers J, et al. Identification of stem cells in small intestine and colon by marker gene Lgr5. *Nature.* 2007;449:1003-1007. DOI: 10.1038/nature06196. PMID: 17934449.
23 Neophytou C, Pitsouli C. How Gut Microbes Nurture Intestinal Stem Cells: A Drosophila Perspective. *Metabolites*. 2022;12:169. DOI: 10.3390/metabo12020169. PMID: 35208243.

24 Alonso S, Yilmaz OH. Nutritional regulation of intestinal stem cells. *Annu Rev Nutr*. 2018;38:273-301. DOI: 10.1146/annurev-nutr-082117-051644. PMID: 29799767.
25 Wang D, Li P, Odle J, e al. Modulation of intestinal stem cell homeostasis by nutrients: a novel therapeutic option for intestinal diseases. *Nutr Res Rev*. 2021;1-9. DOI: 10.1017/S0954422421000172. PMID: 34100341.
26 O'Brien LE, Soliman SS, Li X, et al. Altered modes of stem cell division drive adaptive intestinal growth. *Cell*. 2011;147:603-614. DOI: 10.1016/j.cell.2011.08.048. PMID: 22036568.
27 Gashmardi N, Mehrabani D, Kkodabandeh Z, et al. Effect of bone marrow-derived mesenchymal stem cells on changes of serum levels of tnf-α and locomotor function after spinal cord injury in mice. *J Med Sci*. 2016;16:16-24. DOI: 10.3923/jms.2016.16.24.
28 Iravani K, Mehrabani D, Doostkam A, et al. Use of Magnetic Resonance Imaging to Assess the Regenerative Effects of Adipose Tissue-Derived Mesenchymal Stem Cells in a Rabbit Cartilaginous Laryngeal Defect Model. *Curr Ther Res Clin Exp*. 2022;97:100682. DOI: 10.1016/j.curtheres.2022.100682. PMID: 35959231.
29 Anari L, Mehrabani D, Nasiri M, et al. in Vitro Effect of Methamphetamine on Proliferation, Differentiation and Apoptosis of Adipose Tissue Stem Cells. *J Pharm Pharm Sci*. 2022;25:69-76. DOI: 10.18433/jpps31843. PMID: 35030074.
30 Rasekh H, Hoseini Farahi M, Mehrabani D, et al. Proliferative and Regenerative Effect of Acetonic Extract of Feijoa sellowiana on Stem Cells. *World J Plast Surg*. 2020;9:313-320. DOI: 10.29252/wjps.9.3.313. PMID: 33330009.
31 Mehrabani D, Khajehahmadi Z, Tajik P, et al. Regenerative Effect of Bone Marrow-derived Mesenchymal Stem Cells in Thioacetamide-induced Liver Fibrosis of Rats. *Arch Razi Inst*. 2019;74:279-286. DOI: 10.22092/ari.2018.110029.1120. PMID: 31592593.
32 Hashemi SS, Mohammadi AA, Kabiri H, et al. The healing effect of Wharton's jelly stem cells seeded on biological scaffold in chronic skin ulcers: A randomized clinical trial. *J Cosmet Dermatol*. 2019;186:1961-67. DOI: 10.1111/jocd.12931. PMID: 31127705.
33 Mohammadzadeh N, Mehrabani D, Zare S, et al. What Happens When Methamphetamine Is Added to Nutrients of Cell Culture Medium? In Vitro Assessment of Morphological, Growth and Differential Potential of Wharton's Jelly Stem Cells. *Int J Nutr Sci*. 2022;74:233-240. DOI: 10.30476/IJNS.2022.97432.1210.
34 Mehrabani D, Nazempour M, Mehdinavaz-Aghdam R, et al. MRI tracking of human Wharton's jelly stem cells seeded onto acellular dermal matrix labeled with superparamagnetic iron oxide nanoparticles in burn wounds. *Burns Trauma*. 2022;10:tkac018. DOI: 10.1093/burnst/tkac018. PMID: 36380853.
35 Fard M, Akhavan-Tavakoli M, Khanjani S, et al. Bilayer Amniotic Membrane/Nano-fibrous Fibroin Scaffold Promotes Differentiation Capability of Menstrual Blood Stem Cells into Keratinocyte-Like Cells. *Mol Biotechnol*. 2018;60:100-110. DOI: 10.1007/s12033-017-0049-0. PMID: 29247317.
36 Khajehahmadi Z, Mehraban D, Ashraf MJ, et al. Healing effect of conditioned media from bone marrow-derived stem cells in thioacetamide-induced liver fibrosis of rat. *J Med Sci*. 2016;161-2:7-15. DOI: 10.3923/jms.2016.7.15.
37 Payehdar A, Hosseini SE, Mehrabani D, et al. Healing effect of conditioned medium of adipose tissue-derived mesenchymal stem cells on histomorphometric changes of mice testis in busulfan induced-azoospermia model. *Horizon Med Sci*. 2017;233:235-42.
38 Jahromi IR, Mehrabani D, Mohammadi A, et al. Emergence of signs of neural cells after exposure of bone marrow-derived mesenchymal stem cells to fetal brain extract. *Iran J Basic Med Sci*. 2017;20:301-307. DOI: 10.22038/ijbms.2017.8360. PMID: 28392903.
39 Sedighi A, Mehrabani D, Shirazi R. Histopathological evaluation of the healing effects of human amniotic membrane transplantation in third-degree burn wound injuries. *Comp Clin Pathol*. 2016;25:381-5. DOI: 10.1007/s00580-015-2194-9.
40 Mehrabani D, Mojtahed Jaberi F, Zakerinia M, et al. The Healing Effect of Bone Marrow-Derived Stem Cells in Knee Osteoarthritis: A Case Report. *World J Plast Surg*. 2016;5:168-74. PMID: 27579273.
41 Rasekh H, Mehrabani D, Farahi MH, et al. Screening of Feijoa (Acca Sellowiana (O. Berg) Burret) Fruit Effect on Proliferation and Apoptosis using Bone Marrow derived Stem Cells Model. *Electron J Gen Med*. 2020;17:em269. DOI: 10.29333/ejgm/8458.
42 Aghamir SM, Mehrabani D, Amini M, et al. The Regenerative Effect of Bone Marrow-Derived Stem Cells on Cell Count and Survival in Acute Radiation Syndrome. *World J Plast Surg*. 2017;6:111-113. PMID: 28289623.
43 Borzou B, Mehrabani D, Zare S, et al. The

Effect of Age and Type of Media on Growth Kinetics of Human Amniotic Fluid Stem Cells. *Biopreserv Biobank*. 2020;18:389-394. DOI: 10.1089/bio.2019.0103. PMID: 32799559.

44 Mehrabani D, Arshi S, Sadeghi L, et al. The Ameliorating Effect of Adipose Tissue Stem Cells on Liver Function in Experimental Rats with Liver Fibrosis. *Int J Nutr Sci*. 2022;7:225-232. DOI:10.30476/IJNS.2022.97438.1211.

45 Sadraei MR, Mehrabani D, Tanideh N, et al. Bone marrow stem cell implant for articular cartilage defects in Guinea pigs. *Onl J Vet Res*. 2020;24:438-448.

46 Wu J, Niu P, Zhao Y, et al. Impact of miR-223-3p and miR-2909 on inflammatory factors IL-6, IL-1ß, and TNF-α, and the TLR4/TLR2/NF-κB/STAT3 signaling pathway induced by lipopolysaccharide in human adipose stem cells. *PLoS One*. 2019;14:e0212063. DOI: 10.1371/journal.pone.0212063. PMID: 30807577.

47 D'Esposito V, Ambrosio MR, Liguoro D, et al. In severe obesity, subcutaneous adipose tissue cell-derived cytokines are early markers of impaired glucose tolerance and are modulated by quercetin. *Int J Obes*. 2021;45:1811-1820. DOI: 10.1038/s41366-021-00850-1. PMID: 33993191.

48 Shin S, El-Sabbagh AS, Lukas BE, et al. Adipose stem cells in obesity: Challenges and opportunities. *Biosci Rep*. 2020;40:BSR20194076. DOI: 10.1042/BSR20194076. PMID: 32452515.

49 Zakaria N, Yahaya BH. Adipose-Derived Mesenchymal Stem Cells Promote Growth and Migration of Lung Adenocarcinoma Cancer Cells. *Adv Exp Med Biol.* 2020;1292:83-95. DOI: 10.1007/5584_2019_464. PMID: 31916234.

50 Gyllenhammer LE, Duensing AM, Keleher MR, et al. Fat content in infant mesenchymal stem cells prospectively associates with childhood adiposity and fasting glucose. *Obesity (Silver Spring).* 2023;31:37-42. DOI: 10.1002/oby.23594. PMID: 36541155.

51 Rafalski VA, Mancini E, Brunet A. Energy metabolism and energy-sensing pathways in mammalian embryonic and adult stem cell fate. *J Cell Sci*. 2012;125:5597-5608. DOI: 10.1242/jcs.114827. PMID: 23420198.

52 Ghosh-Choudhary S, Liu J, Finkel T. Metabolic Regulation of Cell Fate and Function. *Trends Cell Biol*. 2020;30:201-212. DOI: 10.1016/j.tcb.2019.12.005. PMID: 31983571.

53 Novak JSS, Baksh SC, Fuchs E. Dietary interventions as regulators of stem cell behavior in homeostasis and disease. *Genes Dev.* 2021;35:199-211. DOI: 10.1101/gad.346973.120. PMID: 33526586.

54 Alvina FB, Gouw AM, Le A. Cancer Stem Cell Metabolism. *Adv Exp Med Biol.* 2021;1311:161-172. DOI: 10.1007/978-3-030-65768-0_12. PMID: 34014542.

55 Puca F, Fedele M, Rasio D, et al. Role of Diet in Stem and Cancer Stem Cells. *Int J Mol Sci.* 2022;23:8108. DOI: 10.3390/ijms23158108. PMID: 35897685.

56 Lu V, Roy IJ, Teitell MA. Nutrients in the fate of pluripotent stem cells. *Cell Metab.* 2021;33:2108-2121. DOI: 10.1016/j.cmet.2021.09.013. PMID: 34644538.

57 Bjerkvig R, Tysnes BB, Aboody KS, et al. The origin of the cancer stem cell: Current controversies and new insights. *Nat Rev Cancer.* 2005;5:899-904. DOI: 10.1038/nrc1740. PMID: 16327766.

58 Baksh SC, Todorova PK, Gur-Cohen S, et al. Extracellular serine controls epidermal stem cell fate and tumour initiation. *Nat Cell Biol.* 2020;22:779-790. DOI: 10.1038/s41556-020-0525-9. PMID: 32451440.

59 Yilmaz ÖH, Katajisto P, Lamming DW, et al. mTORC1 in the Paneth cell niche couples intestinal stem-cell function to calorie intake. *Nature*. 2012;486:490–495. DOI: 10.1038/nature11163. PMID: 22722868.

60 Smith J, Ladi E, Mayer-Proschel M, et al. Redox state is a central modulator of the balance between self-renewal and differentiation in a dividing glial precursor cell. *Proc Natl Acad Sci USA*. 2000;97:10032-10037. DOI: 10.1073/pnas.170209797. PMID: 10944195.

61 Liu J, Qin X, Pan D, et al. Amino Acid-Mediated Metabolism: A New Power to Influence Properties of Stem Cells. *Stem Cells Int*. 2019;2019:6919463. DOI: 10.1155/2019/6919463. PMID: 31885621.

62 Taya Y, Ota Y, Wilkinson AC, et al. Depleting dietary valine permits nonmyeloablative mouse hematopoietic stem cell transplantation. *Science*. 2016;354:1152-1155. DOI: 10.1126/science.aag3145. PMID: 27934766.

63 Nikolits I, Nebel S, Egger D, et al. Towards Physiologic Culture Approaches to Improve Standard Cultivation of Mesenchymal Stem Cells. *Cells*. 2021;10:886. DOI: 10.3390/cells10040886. PMID: 33924517.

64 Wang D, Odle J, Liu Y. Metabolic regulation of intestinal stem cell homeostasis. *Trends Cell Biol*. 2021;31:325-7. DOI: 10.1016/j.tcb.2021.02.001. PMID: 33648839.

65 Saito Y, Iwatsuki K, Hanyu H, et al. Effect of essential amino acids on enteroids: Methionine deprivation suppresses proliferation and affects differentiation in enteroid stem cells. *Biochem*

Biophys Res Commun. 2017;488:171-6. DOI: 10.1016/j.bbrc.2017.05.029. PMID: 28483523.

66 Obata F, Tsuda-Sakurai K, Yamazaki T, et al. Nutritional control of stem cell division through S-adenosylmethionine in Drosophila intestine. *Dev Cell*. 2018;44:741-751.e3. DOI: 10.1016/j.devcel.2018.02.017. PMID: 29587144.

67 Zhang X, Jin Q, Jin LH. High sugar diet disrupts gut homeostasis though JNK and STAT pathways in Drosophila. *Biochem Biophys Res Commun*. 2017;487:910-916. DOI: 10.1016/j.bbrc.2017.04.156. PMID: 28476621.

68 Walvekar AS, Srinivasan R, Gupta R, et al. Methionine Coordinates A Hierarchically Organized Anabolic Program Enabling Proliferation. *Mol Biol Cell*. 2018;29:3183-3200. DOI:10.1091/ mbc.e18-08-0515. PMID: 30354837.

69 Dai JM, Yu MX, Shen ZY, et al. Leucine Promotes Proliferation and Differentiation of Primary Preterm Rat Satellite Cells in Part through Mtorc1 Signaling Pathway. *Nutrients*. 2015;7:3387-3400. DOI:10.3390/nu7053387. PMID: 26007333.

70 Zhang P, Liang X, Shan T, et al. Mtor Is Necessary for Proper Satellite Cell Activity and Skeletal Muscle Regeneration. Biochem. *Biophysical Res Commun*. 2015;463P:102-108. 3 DOI: 10.1016/j.bbrc.2015.05.032. PMID: 25998386.

71 Hou Q, Dong Y, Yu Q, et al. Regulation of the Paneth cell niche by exogenous L-arginine couples the intestinal stem cell function. *FASEB J*. 2020;34:10299-315. DOI: 10.1096/fj.201902573RR. PMID: 32725957.

72 Hosios AM, Hecht VC, Danai LV, et al. Amino Acids rather Than Glucose Account for the Majority of Cell Mass in Proliferating Mammalian Cells. *Dev Cell*. 2016;36:540-549. DOI:10.1016/j.devcel.2016.02.012. PMID: 26954548.

73 Gaglio D, Soldati C, Vanoni M, et al. Glutamine Deprivation Induces Abortive S-phase Rescued by Deoxyribonucleotides in K-Ras Transformed Fibroblasts. *PLos One*. 2009;4:E4715. DOI:10.1371/journal.pone.0004715. PMID: 19262748.

74 Viitanen AI. Glutamine Control of Intestinal Stem Cells in Drosophila melanogaster. Master's Thesis, University of Helsinki, Helsinki, Finland, 2019.

75 Deng H, Gerencser AA, Jasper H. Signal integration by Ca 2 regulates intestinal stem-cell activity. *Nature*. 2015;528:212-217. DOI: 10.1038/nature16170. PMID: 26633624 PMCID: PMC4669953.

76 Clémot M, Sênos Demarco R, Jones DL. Lipid Mediated Regulation of Adult Stem Cell Behavior. *Front Cell Dev Biol*. 2020;8:115. DOI: 10.3389/fcell.2020.00115. PMID: 32185173.

77 Obniski R, Sieber M, Spradling AC. Dietary lipids modulate Notch signaling and influence adult intestinal development and metabolism in Drosophila. *Dev Cell*. 2018;47:98-111.e5. DOI: 10.1016/j.devcel.2018.08.013. PMID: 30220569.

78 Beyaz S, Mana MD, Roper J, et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. *Nature.* 2016;531:53-58. DOI: 10.1038/nature17173. PMID: 26935695.

79 Li W, Zimmerman SE, Peregrina K, et al. The nutritional environment determines which and how intestinal stem cells contribute to homeostasis and tumorigenesis. *Carcinogenesi*s. 2019;40:937-46. DOI: 10.1093/carcin/bgz106. PMID: 31169292.

80 Richards P, Pais R, Habib AM, et al. High fat diet impairs the function of glucagon-like peptide-1 producing L-cells. *Peptides*. 2016;77:21-27. DOI: 10.1016/j.peptides.2015.06.006. PMID: 26145551.

81 Koh A, De Vadder F, Kovatcheva-Datchary P, et al. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. *Cell*. 2016;165:1332-1345. DOI: 10.1016/j.cell.2016.05.041. PMID: 27259147.

82 Kapinova A, Kubatka P, Golubnitschaja O, et al. Dietary phytochemicals in breast cancer research: Anticancer effects and potential utility for effective chemoprevention. *Environ Health Prev Med*. 2018;23:36. DOI: 10.1186/s12199-018-0724-1. PMID: 30092754.

83 Yagi H, Tan J, Tuan RS. Polyphenols suppress hydrogen peroxide-induced oxidative stress in human bone-marrow derived mesenchymal stem cells. *J Cell Biochem*. 2013;114:1163-1173. DOI:10.1002/jcb.24459. PMID: 23192437

84 Torre E, Iviglia G, Cassinelli C, et al. Polyphenols from grape pomace induce osteogenic differentiation in mesenchymal stem cells. *Int J Mol Med*. 2020;45:1721-1734. DOI: 10.3892/ijmm.2020.4556. PMID: 32236566

85 Bar-El Dadon S, Reifen R. Vitamin A and the epigenome. *Crit Rev Food Sci Nutr.* 2017;57:2404-2411. DOI:10.1080/10408398.2015.1060940. PMID: 26565606.

86 Cañete A, Cano E, Muñoz-Chápuli R, et al. Role of Vitamin A/Retinoic Acid in Regulation of Embryonic and Adult Hematopoiesis. *Nutrients.* 2017;9:159. DOI:10.3390/nu9020159. PMID: 28230720.

87 Cabezas-Wallscheid N, Buettner F, Sommerkamp P, et al. Vitamin A-Retinoic Acid Signaling Regulates Hematopoietic Stem Cell Dormancy.

Cell. 2017;169:807-823.e19. DOI: 10.1016/j.cell.2017.04.018. PMID: 28479188.

88 Sarubbo F, Moranta D, Pani G. Dietary polyphenols and neurogenesis: Molecular interactions and implication for brain ageing and cognition. *Neurosci Biobehav Rev.* 2018;90:456-470. DOI: 10.1016/j.neubiorev.2018.05.011. PMID: 29753753.

89 Dutta D, Dobson AJ, Houtz PL, et al. Regional cell-specific transcriptome mapping reveals regulatory complexity in the adult Drosophila midgut. *Cell Rep*. 2015;12:346-358. DOI: 10.1016/j.celrep.2015.06.009. PMID: 26146076.

90 Neophytou C, Pitsouli C. Biotin Controls Intestinal Stem Cell Mitosis and Host-Microbiome Interactions. *Cell Rep*. 2022;38:110505. DOI: 10.1016/j.celrep.2022.110505. PMID: 35263602.

91 Li P, Wang Y, Li P, et al. Maternal inappropriate calcium intake aggravates dietary-induced obesity in male offspring by affecting the differentiation potential of mesenchymal stem cells. *World J Stem Cells*. 2022;14:756-776. DOI:10.4252/wjsc.v14.i10.756. PMID:36337156.

92 Porro S, Genchi VA, Cignarelli A, et al. Dysmetabolic adipose tissue in obesity: morphological and functional characteristics of adipose stem cells and mature adipocytes in healthy and unhealthy obese subjects. *J Endocrinol Invest*. 2021;44:921-941. DOI:10.1007/s40618-020-01446-8. PMID:33145726.

93 Matsushita K, Dzau VJ. Mesenchymal stem cells in obesity: insights for translational applications. *Lab Invest*. 2017;97:1158-1166. DOI:10.1038/labinvest.2017.42. PMID:28414326.

94 Zhang P, Zhang H, Lin J, et al. Insulin impedes osteogenesis of BMSCs by inhibiting autophagy and promoting premature senescence via the TGF-β1 pathway. *Aging Albany NY*. 2020;12:2084-2100. DOI: 10.18632/aging.102723. PMID:32017705.

95 Chen XR, Bai J, Yuan SJ, et al. Calcium phosphate nanoparticles are associated with inorganic phosphate-induced osteogenic differentiation of rat bone marrow stromal cells. *Chem Biol Interact*. 2015;238:111-117. DOI: 10.1016/j.cbi.2015.06.027. PMID: 26111760.

96 Burgess RJ, Agathocleous M, Morrison SJ. Metabolic regulation of stem cell function. *J Intern Med*. 2014;276:12-24. DOI: 10.1111/joim.12247. PMID: 24697828.

97 Igarashi M, Guarente L. mTORC1 and SIRT1 cooperate to foster expansion of gut adult stem cells during calorie restriction. *Cell*. 2016;166:436-50. DOI: 10.1016/j.cell.2016.05.044. PMID: 27345368.

98 Igarashi M, Miura M, Williams E, et al. NAD+ supplementation rejuvenates aged gut adult stem cells. *Aging Cell*. 2019;18:e12935. DOI: 10.1111/acel.12935. PMID: 30917412.

99 Cheng CW, Biton M, Haber AL, et al. Ketone body signaling mediates intestinal stem cell homeostasis and adaptation to diet. *Cell*. 2019;178:1115-31e15. DOI: 10.1016/j.cell.2019.07.048. PMID: 31442404.

100 Markandey M, Bajaj A, Ilott NE, et al. Gut microbiota: sculptors of the intestinal stem cell niche in health and inflammatory bowel disease. *Gut Microbes*. 2021;131:1990827. DOI: 10.1080/19490976.2021.1990827. PMID: 34747326.