JOURNAL OF COLLEGE OF PALLIATIVE MEDICINE OF SRI LANKA
abhittharetha kalyāṇe

EDITORIAL

DOI: 10.54448/jcpmsl23101

Palliative medicine under the light of regenerative medicine and nutrology: a new paradigm

Idiberto José Zotarelli Filho[1-3]*

[1] International Honorary Professor at the College of Palliative Medicine of Sri Lanka, Colombo, Sri Lanka.
[2] FACERES – Faculty of Medicine of Sao Jose do Rio Preto, Sao Paulo, Brazil.
[3] ABRAN - Associação Brasileira de Nutrologia/Brazilian Association of Nutrology, Catanduva, Sao Paulo, Brazil.

*Corresponding author: Dr. Idiberto José Zotarelli Filho.
FACERES – Faculty of Medicine of Sao Jose do Rio Preto,
Sao Paulo, Brazil.
Email: dr.idibertozotarelli@faceres.com.br
DOI: https://doi.org/10.54448/jcpmsl23101
Received: 01-20-2023; Revised: 03-10-2023; Accepted: 03-12-2023; Published: 03-16-2023; JCPMSL-id: e23101

Palliative care (PC) is active and comprehensive care provided to people with a serious, progressive illness that threatens the continuity of their lives. Promote the quality of life of patients and their families through the prevention and relief of suffering, early identification of potentially treatable situations, and careful and thorough assessment and treatment of pain and other physical, social, psychological, and spiritual symptoms [1].

Also, PC can be associated with treatment to cure the disease to help manage symptoms that are difficult to control and improve the clinical conditions of the patient. As the disease progresses, even in the presence of treatment with curative intent, the palliative approach should be expanded to also take care of the psychological, social, and spiritual aspects [2].

In the terminal phase, in which the patient has little time to live, palliative treatment becomes a priority to ensure quality of life, comfort, and dignity. The transition from care with a cure objective to care with palliative intent is a continuous process, and its dynamics differ for each patient [1,2].

In this regard, regenerative medicine and nutrology can play an important role in palliative care, especially in improving the quality of life of patients [3-6]. In this sense, it is emphasized that 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 body's energy balance and nutritional status [3].

The metabolic by-products and substrates that regulate epigenetic and signaling pathways are considered to play an instructive rather than an observer role in regulating cell fate decisions. Scientific evidence from randomized clinical trials and meta-analyses shows that nutritional health acts on regenerative processes. Metabolism encompasses the interactions between diet, the microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to sustain 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 [7].

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact the cellular state by modulating signaling pathway activity. A clear example is through the mechanistic targeting of the rapamycin (mTOR) signaling pathway and, in particular, the mTOR complex 1 (mTORC1), which regulates cell growth only when nutrients and growth factors are present [7].

Furthermore, depletion of specific nutrients including arginine, leucine, and Sadenosyl methionine prevents growth factor-induced activation of mTORC1 by blocking Rag GTPase-mediated recruitment of mTORC1 to the lysosome where it can be activated by Rheb GTPase. Another way that nutrients are sensed to impact cellular status is through AMP-activated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance and in the process regulates cell growth. and autophagy. Transcription factors can be directly regulated by metabolites [7].

As a corollary, dietary manipulations and

metabolites can affect tissue stem cells and drive cell fate decisions, as highlighted in the small intestine (intestinal stem cells (ISC)), hematopoietic system (HSCs), liver, muscle (muscle stem cells/satellite stem cells (SCs)). HSC self-renewal and differentiation can be regulated by manipulating vitamin C, A, or D levels. HSC self-renewal is also impaired by valine restriction [5].

In this context, nutritional health acts directly on the human intestinal microbiota, impacting metabolism and the immune system for tissue regeneration. Recent findings on the role of the "nutritional microbiota" in mechanisms involved in tissue regeneration, in particular, skin, liver, bone, and nervous system regeneration [8].

Based on this, in the inflammatory phase, vitamin A increases cytokine release, 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 role key role in wound scar stabilization [9]. Therefore, nutritional status and inflammation have recently been identified as regulators of stem cell activity in the mammalian gut, and we explored how these systemic signals might influence homeostasis and regeneration [10].

One study demonstrated that the expression of the enzyme Hmgcs2, which regulates the ratio-limiting step in ketone body synthesis, is enriched in LGR5+ ISCs. Loss of Hmgcs2 impairs ISC regeneration and promotes promiscuous differentiation to the Paneth cell line. Mechanistically, the β-hydroxybutyrate ketone body inhibits class I histone deacetylases to enhance transcriptional activation of Notch signaling and maintain stem cell self-renewal [11].

Furthermore, age-related reduction in muscle repair efficiency contributes to the development of sarcopenia. Nutrients such as amino acids, polyunsaturated fatty acids, polyphenols, and vitamin D can enhance skeletal muscle regeneration by targeting key functions of immune system cells, muscle cells, or both [12].

Finally, growing evidence suggests that metabolism during quiescence, activation, and differentiation may vary between tissues, integrating signaling cues and metabolic inputs with the release of exosomes and microRNAs as important metabolic messengers in the body, this process is strongly regulated by nutrients. Nutrient-mediated metabolomics provides information on cellular pathways, looking at substrates and metabolic products through different pathways [13]. Along with transcriptomics and proteomics analysis, it is observed that metabolism can affect cell fate (and vice versa) [14].

Acknowledgement
Not applicable.

Ethics 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. Havyer RD, Abedini N, Jayes RL, Matti-Orozco B, Pomerantz DH, Ansari AA. Palliative care: An update for internists. Cleve Clin J Med. 2022 May 2;89(5):262- 268. doi: 10.3949/ccjm.89a.21075.
2. Glajchen M, Goehring A, Johns H, Portenoy RK. Family Meetings in Palliative Care: Benefits and Barriers. Curr Treat Options Oncol. 2022 May;23(5):658-667. doi: 10.1007/s11864-022-00957-1.
3. Yamagishi H, Shigematsu K. Perspectives on Stem Cell-Based Regenerative Medicine with a Particular Emphasis on Mesenchymal Stem Cell Therapy. JMA J. 2022 Jan 17;5(1):36-43. doi: 10.31662/jmaj.2021-0080.
4. Kornicka K, Kocherova I, Marycz K. The effects of chosen plant extracts and compounds on mesenchymal stem cells-a bridge between molecular nutrition and regenerative medicine-concise review. Phytother Res. 2017

Jul;31(7):947-958. doi: 10.1002/ptr.5812. Epub 2017 Apr 25. PMID: 28439998.

5. Rose LF, Wolf EJ, Brindle T, Cernich A, Dean WK, Dearth CL, Grimm M, Kusiak A, Nitkin R, Potter K, Randolph BJ, Wang F, Yamaguchi D. The convergence of regenerative medicine and rehabilitation: federal perspectives. NPJ Regen Med. 2018 Oct 10;3:19. doi: 10.1038/s41536-018-0056-1. PMID: 30323950; PMCID: PMC6180133.
6. Lüscher TF. Novel prognostic markers and treatment options in heart failure: from palliative to regenerative medicine. Eur Heart J. 2015 Mar 21;36(12):699-701. doi: 10.1093/eurheartj/ehv040. PMID: 25796086.
7. 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.
8. Shavandi A, Saeedi P, Gérard P, Jalalvandi E, Cannella D, Bekhit AE. The role of microbiota in tissue repair and regeneration. J Tissue Eng Regen Med. 2020 Mar;14(3):539-555. doi: 10.1002/term.3009. Epub 2020 Jan 15. PMID: 31845514.
9. Palmieri B, Vadalà M, Laurino C. Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. J Wound Care. 2019 Oct 2;28(10):683-693. doi: 10.12968/jowc.2019.28.10.683. PMID: 31600106.
10. Beumer J, Clevers H. Regulation and plasticity of intestinal stem cells during homeostasis and regeneration. Development. 2016 Oct 15;143(20):3639-3649. doi: 10.1242/dev.133132. PMID: 27802133.
11. Cheng CW, Biton M, Haber AL, Gunduz N, Eng G, Gaynor LT, Tripathi S, Calibasi-Kocal G, Rickelt S, Butty VL, Moreno-Serrano M, Iqbal AM, BauerRowe KE, Imada S, Ulutas MS, Mylonas C, Whary MT, Levine SS, Basbinar Y, Hynes RO, Mino-Kenudson M, Deshpande V, Boyer LA, Fox JG, Terranova C, Rai K, Piwnica-Worms H, Mihaylova MM, Regev A, Yilmaz ÖH. Ketone Body Signaling Mediates Intestinal Stem Cell Homeostasis and Adaptation to Diet. Cell. 2019 Aug 22;178(5):1115-1131.e15. doi: 10.1016/j.cell.2019.07.048.
12. Domingues-Faria C, Vasson MP, Goncalves-Mendes N, Boirie Y, Walrand S. Skeletal muscle regeneration and impact of aging and nutrition. Ageing Res Rev. 2016 Mar;26:22-36. doi: 10.1016/j.arr.2015.12.004.
13. Rinschen MM, Ivanisevic J, Giera M, Siuzdak G. Identification of bioactive metabolites using activity metabolomics. Nat Rev Mol Cell Biol. 2019 Jun;20(6):353-367. doi: 10.1038/s41580-019-0108-4.
14. Agathocleous M, Meacham CE, Burgess RJ, Piskounova E, Zhao Z, Crane GM, Cowin BL, Bruner E, Murphy MM, Chen W, Spangrude GJ, Hu Z, DeBerardinis RJ, Morrison SJ. Ascorbate regulates haematopoietic stem cell function and leukaemogenesis. Nature. 2017 Sep 28;549(7673):476-481. doi: 10.1038/nature23876.