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Review Article

Can intermittent fasting help in stem-cell rejuvenation?

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Abstract

Background: Human tissues are sustained by stem cells, the balance between stem cell self-renewal and differentiation, and cell death is the crucial element of haemostasis, which plays a vital role in tissue remodelling. Stem cell therapy is recognized as regenerative medicine. We can stimulate stem cell growth/regeneration through various events.

Objectives: In this review, we illustrate whether fasting can stimulate stem cell regeneration.

Methodology: A literature survey was undertaken to gather recent research and address the effects of fasting on stem cell renewal, which was the review's purpose.

Results: Enterocytes in drosophila were restored after exposure to the dietary restriction. As the result, fasting before etoposide exposure safeguarded mice against harm caused by etoposide when compared with the fed group. A study conducted on the effects of periodic fasting in yeast, mice, and humans shows the increase in lifespan and stress resistance of yeast fasting reduces the risks due to age factors and diseases like diabetes, cardiovascular diseases and promotes a healthy life span of mice and human.

Conclusion: Dietary limitations will be used in conjunction with the existing therapeutic approach as adjuvant therapy. It will be a more effective treatment. Fasting has the potential to protect against the negative effects of chemotherapy while also boosting stem cell regeneration, according to preclinical findings. Even though regenerative medicine and stem cell therapy are still in their embryonic stage, greater interventions are needed to show the target pathway of fasting in stem cell renewal.

Keywords: Fasting, stem cell regeneration, emerging therapy.

1. INTRODUCTION:

1.1 Stem cells:

Hematopoietic stem cells circulate in the absence of stimulation at a relatively low frequency ($\sim 3/\mu\text{l}$) in circulation ¹. When a person is injured or inflamed, an enormous number of stem cells are released ². Endocrine and metabolic ailments, on the other hand, are linked with substantial reductions in the number of circulating stem cells that have been seen, as perceived in the cases of diabetes and acromegaly ³. In humans, tissues are sustained by stem cells which possess 2 characteristics

- The capability of self-renew and generation
- Capacity to distinguish into progenitor cells

Hematopoietic stem cells (HSC) present in the bone marrow give rise to mature cells, those cells had inestimable functions such as muscle regeneration mediated by satellite cells which restores muscle, when muscle injury occurs, from HSC myeloid, lymphoid, erythroid blood cells, are matured.

Neural stem cells in CNS & PNS which is necessary for many spontaneous functions like memory, GI motility during foetal development.

The balance between stem cell self-renewal and differentiation and cell death is the crucial element of haemostasis ⁴. Haemostasis of stem cells plays a vital role in tissue remodelling against damaged tissues.

Stem cell therapy which is an emerging treatment method also recognized as regenerative medicine, now a day's stem cell therapy is supplanting certain chemotherapy strategies. One of the therapy for cancer management along with stem cell stimulation results in enhanced resistance to chemotherapy toxicity and aging-related diminishing through decreased IGF 1/PKA signalling thus resulting in the safeguarding of haemostasis. We can stimulate stem cell growth/regeneration through various events. In this review, we expound on whether fasting can stimulate stem cell regeneration ⁵.

1.2 Fasting:

Fasting term states that self-denial from food/ drink/both aims for health, religious, health or ethical benefits.

Fasting has been practiced for many years, now a day's physician globally acclaims fasting for health benefits. On the

other hand followers of numerous religions/devotees practice fasting in seasonal or periodic intervals. Fasting is also expressed against defilements of ethical principles in the social order.

We need to glance at the terms like fasting and calorie restriction.

Calorie restriction	Fasting
20-40% lessening of calorie ingestion over some time	Complete avoidance of energy intake for projected interval
Intermittent calorie restriction: 50-70% reduction of calorie ingestion for the squat period	Intermittent fasting: Overall evasion of energy consumption for several hours or alternating a fasting day with an average energy intake a day ⁶ .

Types of fasting:

Fasting can be classified based on objective, advantage or, duration,

Medical fasting:

Fasting has been used since the Hippocrates era as a healing approach for certain symptoms of illness. In this nature of fasting, the diet control may be based on age, sex, and activity.

E.g.: Calorie restriction rallies the outcomes in glucose intolerance conditions,

In the DASH diet plan, salt restriction and calorie restriction lessens the elevated blood pressure points.

Religious fasting:

From the ancient age till nowadays fasting is practiced as a dedication of devotees, usually, religious fasting will be periodic practice like in India Hindus admire fasting on different events. In the Islam community exercise of fast in the month of Ramadhan usually, a whole day fasting from dawn to dusk. Western religions like Christianity empathize with fasting on occasions like Good Friday. Buddhist monks fast as part of their meditation practices. These fasts based on the occasion among religions are believed to have various health and spiritual benefits.

Fasting as a form of protest:

Every so often fasting is used to express social and political views against abuse of ethics.

Classifying fasting based on the duration followed as:

Occasional short fast:

Denying the intake of food for the desired duration last on definite occasion like festivals or for treatment purpose. It is insignificant because it is a tiny duration.

Intermittent fast:

Another type of fasting for desired period/ alternate day or duration where desist from food for some benefits. Intermittent fasting along with medication/therapy/exercise will be more profited ⁷.

Some additional forms of fasting are:

- Time-restricted fasting
- Overnight fasting
- Eat stop eat
- Whole day fasting
- Alternate day fasting
- Choose your day fasting

Performing the fasting for health were benefitted some metabolic syndromes/ disorders/diseases like PCOS, Diabetes, Cancer, etc ⁸.

2. METHODOLOGY:

A literature survey was undertaken to gather recent research and address the effects of fasting on stem cell renewal, which was the review's purpose.

3. BENEFITS OF FASTING ON COMMON CONDITIONS**3.1 Intermittent fasting and PCOS:**

Poly Cystic Ovary Syndrome (PCOS) is a common endocrine disorder among women characterized by the parameters like oligo ovulation, hyperandrogenism, the existence of 12 or more follicles in each ovary 2-9mm diameter, and increased ovary volume, etc. PCOS can lead to infertility, insulin resistance which can be cured by an alternative approach such as fasting. In PCOS ovaries bind with insulin growth factor - 1 (IGF-1) receptors through fasting circulating levels of IGF-1 and also improve hyperandrogenism, due to weight loss as a result of fasting shrinks adipose tissue and may negatively modulate the conversion of androgen. PCOS is classified based on phenotypes, fasting plans like intermittent fasting (IF) and periodic fasting (PF) like the insulin resistance diet probably had the most striking beneficial effects on PCOS particularly in type A phenotype ⁹.

3.2 Role of intermittent fasting in treating diabetes:

A case series by Furmli et al. conducted 24-hour fasts thrice a week in three patients with type 2 diabetes, after beginning the fasting regimen all patients had a significant reduction in HbA1C, weight within 1 month they were capable to discontinue the insulin in their treatment.

Added clinical trial which includes 137 adults with type 2 diabetes distributed into 2 groups one with intermittent energy restriction group (500-600 kcal/day for 2 days/week and normal diet every other day) and a constant energy restriction group (1200-1500 kcal/day), for 1 year period both groups had fall in HbA1C and greater decline of weight in the second group, thereby fasting has the wide benefit on diabetes by reducing insulin resistance both study suggests that fasting can be a complementary therapy for metabolic diseases along with required medication ¹⁰.

3.3 Fasting can aid cancer and cancer therapy:

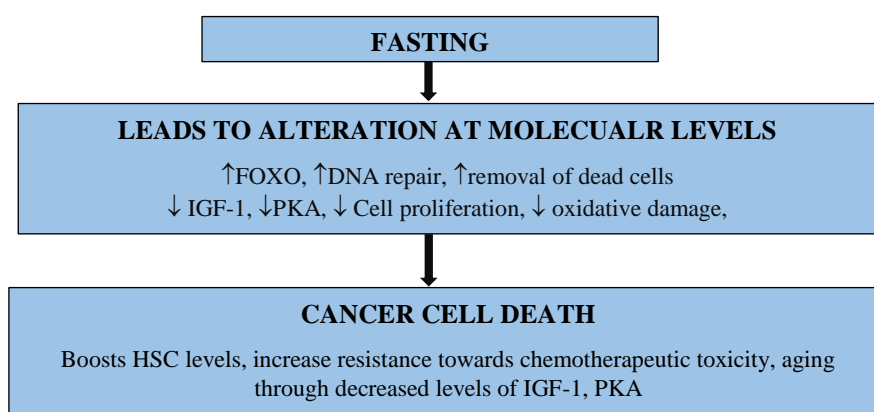
Cancer cells rely on oxygen-dependent glycolysis as their primary source of energy. As an outcome, tumors require a steady supply of glucose and nutrients and are extremely

vulnerable to diet shortage¹¹. Fasting can lead to cellular stress thus stress can induce adaptations, without leading to malnutrition such adaptation diverts the energy for protective functions and minimize damages due to oxidative stress. Restricted calorie intake causes several metabolic adaptations like decreasing the level of IGF-1, insulin, oxidative stress, inflammation which leads to cellular/molecular adaptation like increased FOXO, PTEN, DNA repair, removal of dead cells decreases the cell proliferation, oxidative damage, finally reduce the incidence of cancer. Chemotherapy effects can be improved by fasting. Treatment of malignancies with the caloric-restriction mimetic (CRM), hydroxycitrate, or fasting would boost tumor autophagy and improve responses to immunogenic chemotherapies. Reduced appetite, nausea, vomiting, diarrhea, and cachexia are common signs in patients who have been treated with these drugs¹². Fasting also benefitted in protecting against treatment-associated side effects triggered due to cancer or radiation therapy without altering the therapeutic activity, recent studies conclude that cancer patients undergoing chemotherapy experience undesired side effects and morbidity which can be reduced by short-term fasting before chemotherapy. Fasting hereby acts as a shield against toxicity due to chemotherapy¹³.

3.4 How fasting protects stem cells from chemotherapeutic agents:

The study on mice by Raffaghello et al., states that for six cycles (12 weeks) of fasting in combination with cyclophosphamide (CP) treatment, mice were secured from chemotherapy-induced death. Fasting preserved the

animals' L/M proportion, peripheral WBC. Each cycle began with a two-day water-only fast immediately before beginning CP therapy, followed by two weeks of unlimited food availability. In Phase I clinical trial for safety and feasibility, human patients fasted for 72 hours before receiving platinum-based chemotherapy showed similar protection against peripheral WBC reduction and preservation of the L/M ratio¹⁴. Previous identifications demonstrated that reduced IGF-1 levels have a key role in chemo-toxicity resistance. They used mice with defective growth hormone receptor (GHR) signaling upstream of IGF-1 synthesis to confirm the importance of diminished IGF-1 signaling specifically in bone marrow (BM). In the absence of PC treatment, these mice had lower levels of IGF-1 in circulation and the BM, as well as properties analogous to WT mice exposed to fasting cycles, such as diminished BM DNA destruction and maintenance of circulating WBC numbers and L/M relations, and augmented numbers of cycling HSCs and preservation of L/M ratios as a function of age. Finally, the researchers discovered PKA to be a key downstream target of IGF-1R signaling in HSC self-renewal induced by fasting. In ex vivo BM cultures, siRNA restriction of IGF-1R or PKA boosted HSC reproduction regardless of nutrient/energy intake and enabled effective BM reconstitution in vivo. Although PKA and its target, CREB, can inhibit FoxO1, a key regulator of stress tolerance and stem cell pluripotency, they can also promote it¹⁵. Future research on the influence of dietary modification on T cell function and in combination with other immunotherapies will be crucial in understanding what therapeutic impact these therapies may have in oncology¹⁶



4. EFFECT OF DIETARY RESTRICTIONS ON STEM CELLS:

When food is sufficient, intestinal stem cells in the adult *Drosophila* gut perceive a dietary stimulus to "break homeostasis" and promote growth. SC control a growth program by two changed modes of behavior: enhanced division rates and superiority of symmetric division outcomes, which are driven in part by niche insulin production. When these modified modes are combined, they result in a significant increase in total enterocytes, which is restored when food is absent. As a result, tissue regeneration processes aren't bound by cellular homeostasis; SC can rebuild organs in response to physiological cues¹⁷.

On an observation, mice were allowed to feed ad libitum otherwise fasted for 24 hours before getting administered with etoposide. Food was administered promptly after etoposide administration in all studies. Following etoposide injection, fed mice expired between days 5 and 6, whereas

starved mice lasted, Body mass and dietary intake were assessed daily to determine general health. Post etoposide treatment, fed mice's food intake and weight decreased constantly and significantly. Further investigation found that the SI mucosa of fed mice subjected to high etoposide exhibited severe atrophy 4 days after administration, including villus shrinking, crypt drop out, decreased proportion of epithelial cells per crypt, and total small intestine (SI) length reduces. In contrast to their saline-treated fed equivalents, etoposide-treated fasted rats revealed SI hypertrophic crypts all across the small intestines. By 10 days after etoposide administration, the hypertrophy in SI crypts had disappeared. The two fasted test subjects had identical crypt numbers and villi heights, the depth of the intestinal mucosal lining was retained in etoposide-treated mice, independent of the feeding plan. Independent of the feeding plan, the depth of the intestinal mucosal lining was retained in etoposide-treated mice. In both fed and fasted groups, investigation of the other organs

revealed no clear gross or microscopic anomalies. As a result, fasting before etoposide exposure safeguarded mice against SI harm caused by etoposide. Authors monitored the survival of SI stem cells in fed and fasted mice post etoposide exposure by defining cultures of fast cycling, Lgr5+ stem cell filled epithelial spheroids from injected mice to verify calorie restriction safeguards of SI stem cells in the absence of tamoxifen-mediated lineage recording. To encourage the formation of mouse intestinal epithelial spheroids enriched for stem cells, prepared media with Wnt3a, R-spondin 3, and Noggin was utilized. Stem cells do not develop into the organoid/bud-like forms found in other procedures under similar growth conditions. SI crypts extracted from mice that had been fasting before etoposide treatment produced much more stem cell enhanced epithelial spheroids than mice that were fed. Microarray analysis of mRNAs recovered by laser microdissection of the bottom quarter of SI crypts was used to discover paths that were changed in response to etoposide dosing in fed vs fasted mice. This region is rich in stem cells and Paneth cells that have reached the end of their differentiation. 3 hours after etoposide therapy, we evaluated gene expression in crypt base cells from fed and fasting animals. In addition, starved mice were shown to have genes for stress response, DNA repair, and DNA damage response [IV]. An experimental study on calorie-restricted mice regarding intestinal repair by Richmond et al. found that fasting-induced intestinal regeneration is aided by dormant stem cells (d-ISCs). Reduced nutrition causes transient PTEN suppression and an increase in the number of d-ISCs. The d-ISCs responses are mediated by cell-autonomous stimuli of PI3K→AKT→mTORC1 signaling. PTEN is vital for the regulation of d-ISC and intestinal rejuvenation¹⁸.

Another study conducted by Yilmaz et al. shows that long-term dietary restriction (DR) of (4 to 28 weeks) reduces the size of the intestine and the height of the intestinal villi in mice, but it exploits the pool of ISCs and Paneth cells. This is related to the rise in such cells' potential to develop organoids in culture, indicating improved ISC activity. This trait is caused by DR-mediated suppression of mechanistic targets of rapamycin complex 1 (mTORC1) in Paneth cells. Increased expression of bone stromal antigen 1 (Bst-1), an ectoenzyme that produces the paracrine factor cyclic ADP ribose (cADPR), which rallies the ability of SCs to make organoids, is linked to reduced mechanistic target of rapamycin (mTORC1)¹⁹.

In contrast to fasting, one of the studies correlates fat diet and tumorigenesis, by Beyaz et al. delves into the impact of a high-fat diet (HFD) on the intestinal stem cell (ISC) lineage, revealing a way by which progenitor cells fed to with an HFD develop more stem-like and liable to oncogenic conversion. Beyaz and co-workers observed an increase in the ISC pool, their tendency to form organoids in culture, and their tumors' growth after exposing mice to a longstanding HFD (9 to 14 months). HFD-fed animals had around 50 percent more ISCs expressing olfactomedin4 (olfm4) and, remarkably, about 23 percent fewer Paneth cells than mice fed ad libitum with a conventional diet. In the absence of Paneth cells, these ISCs generated organoids more competently in culture. These results suggest how HFD induces peroxisome proliferator-activated receptor delta (PPAR-d) activation affects not just the activity as well as the ability of intestinal stem and progenitor cells to develop malignancies²⁰.

Every four to five days, the epithelium of the small intestine self-renewal. Intestinal stem cells (Lgr5+ crypt base columnar cells (CBCs)) maintain this regeneration and sit at the base of the intestinal crypt between terminally developed Paneth cells. Newly separated Lgr5+ CBCs and Paneth cells

from the mice intestinal tract have various metabolic pathways, as seen here. Lgr5+ CBCs have higher mitochondrial function than Paneth cells. Suppression of mitochondrial function in Lgr5+ CBCs or glycolysis suppression in Paneth cells has a significant impact on stem cell mechanism, as seen by poor organoid production. Calorie restriction in recent times has been found to raise in the amount of Lgr5+ CBCs and Paneth cells, although the significance of metabolism in intestinal crypt homeostasis is unexplained. Lgr5+ CBCs, Paneth cells, and the residual group of cells (CD24Lgr5) isolated from the intestinal tract of Lgr5-GFP mice had their metabolomes studied. By limiting the electron transport system complex I or IV or ATP synthase, mitochondrial oxidative phosphorylation (OXPHOS) was inhibited, crypt development was decreased. In an organoid model that resembles the formation of the intestinal crypt in vivo, a metabolic shift to mitochondrial OXPHOS is necessary to induce differentiation²¹.

Fasting for a long time affects the activity and characteristics of adult stem cells of Planarians, who are recognized for their fascinating regeneration abilities, may go off nourishment for more than three months without showing any physiologic or activity abnormalities. They deal with extended fasting or malnutrition by decreasing in size, the effect of fasting on planarian stem cells in terms of telomere length was recently revealed²². Telomeres shield chromosomes against DNA damage and ineffective repair mechanisms. Telomeres must have a minimum length that is maintained by telomerase to operate properly. Telomerase activity levels in mature tissues, on the other hand, are insufficient to prevent telomere shortening in aging²³. As a result, telomere length is characterized as a biomarker of aging. We discovered that fasted planarians have a greater proportion of stem cells with longer telomeres, showing that fasting rejuvenates the stem cell pool, the suppression of mTOR signaling, a mechanism is known to improve stem cell activity during the dietary restriction, results in the enrichment of stem cells with long telomeres after fasting. The clearest explanation for how mTOR downregulation lengthens telomeres is through the reduction in mitosis. The cellular response to amputation and blastema growth is known to be regulated by mTOR signaling²⁴. Even though fasting lengthens telomeres, the number of mitotic and stem cells remains unchanged²⁵. "Cell competition" has been connected to mTOR signaling, and autophagy, an mTOR-controlled mechanism, has been demonstrated to be essential for "losing" cells to death. Telomerase activation and long telomere length are recognized to be associated with stem cell pluripotency. We also discovered that fasting enhances the maximal telomere length in planarian stem cells, as well as the fraction of cells containing long telomeres. All of this points to the intriguing possibility that fasting increases pluripotency in planarians through altering mTOR signalling²⁶.

A study conducted on effects of periodic fasting in yeast, mice, and humans shows the increase in lifespan and stress resistance of yeast whereas in mice fast mimicking diet (FMD) exhibits results like regeneration of immunity, lower incidence of cancer, and improves cognitive activity, also increases the life span of mice. In humans, the study shows FMD reduces the risks due to age factors and diseases like diabetes, cardiovascular diseases and promotes a healthy life span²⁷.

Fadini G et al. attempted to characterize the metabolic anomalies related to a low CSC level in greater depth. A cross-sectional survey among 94 healthy men and women, ages 18 to 65, with normal glucose tolerance Blood samples were taken at 0, 10, 20, 30, 60, 90, and 120 minutes from all

subjects during an oral glucose tolerance test (OGTT). Plasma glucose, insulin, C-peptide, and non-esterified fatty acids (NEFA) levels were all studied using mathematical models. A person having low CSCs exhibited a greater NEFA AUC and no notable variations in glucose, insulin, or C-peptide during the OGTT. Other than a drop in the disposition index (DI) in participants with poor CSCs, several insulin sensitivity and beta-cell function indicators were not statistically varied. Elevated NEFA values were linked to CSCs, regardless of age or DI. For the very first time showing lower CSCs are closely linked to excessive NEFA exposures in healthy subjects with normal glucose tolerance. In the perspective of CSCs' prognostic role, the pathological implication of this relationship must be assessed²⁸.

5. CONCLUSION:

Dietary limitations will be used in conjunction with the existing therapeutic approach as adjuvant therapy. It will be a more effective treatment. Fasting has the potential to protect against the negative effects of chemotherapy while also boosting stem cell regeneration, according to preclinical findings. Even though regenerative medicine and stem cell therapy are still in their embryonic stage, greater interventions are needed to show the target pathway of fasting in stem cell renewal.

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REFERENCES:

- Fukuda J, Kaneko T, Egashira M, Oshimi K. Direct Measurement of CD34⁺Blood Stem Cell Absolute Counts by Flow Cytometry. *Stem Cells*. 1998; 16(4):294-300. <https://doi.org/10.1002/stem.160294>
- Fadini G, Ciciliot S, Albiero M. Concise Review: Perspectives and Clinical Implications of Bone Marrow and Circulating Stem Cell Defects in Diabetes. *Stem Cells*. 2016; 35(1):106-116. <https://doi.org/10.1002/stem.2445>
- Fadini G, Dassisti F, Albiero M et al. Endothelial Progenitor Cells Are Reduced in Acromegalic Patients and Can Be Restored by Treatment With Somatostatin Analogs. *The Journal of Clinical Endocrinology & Metabolism*. 2014; 99(12):E2549-E2556. <https://doi.org/10.1210/jc.2014-2275>
- Mihaylova M, Sabatini D, Yilmaz Ö. Dietary and Metabolic Control of Stem Cell Function in Physiology and Cancer. *Cell Stem Cell*. 2014; 14(3):292-305. <https://doi.org/10.1016/j.stem.2014.02.008>
- Hine C, Mitchell J. Saying No to Drugs: Fasting Protects Hematopoietic Stem Cells from Chemotherapy and Aging. *Cell Stem Cell*. 2014; 14(6):704-705. <https://doi.org/10.1016/j.stem.2014.05.016>
- Cancer and Fasting / Calorie Restriction. UCSF Osher Center for Integrative Medicine. <https://osher.ucsf.edu/patient-care/integrative-medicine-resources/cancer-and-nutrition/faq/cancer-and-fasting-calorie-restriction>. Published 2021. Accessed November 10, 2021.
- The Different Types of Fasts. Crosswalk.com. <https://www.google.com/amp/s/www.crosswalk.com/faith/women/the-different-types-of-fasts-11626299.html%3famp=1>. Published 2021. Accessed November 9, 2021.
- Migala J, Kelly Kennedy R. 7 Types of Intermittent Fasting: Which Is Best for You?. *EverydayHealth.com*. <https://www.everydayhealth.com/diet-nutrition/diet/types-intermittent-fasting-which-best-you/>. Published 2021. Accessed November 9, 2021.
- Chiofalo B, Laganà A, Palmara V et al. Fasting as possible complementary approach for polycystic ovary syndrome: Hope or hype?. *Med Hypotheses*. 2017; 105:1-3. <https://doi.org/10.1016/j.mehy.2017.06.013>
- Furmler S, Elmasry R, Ramos M, Fung J. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin. *BMJ Case Rep*. 2018: bcr-2017-221854. <https://doi.org/10.1136/bcr-2017-221854>
- Meynet O, Ricci J. Caloric restriction and cancer: molecular mechanisms and clinical implications. *Trends Mol Med*. 2014; 20(8):419-427. <https://doi.org/10.1016/j.molmed.2014.05.001>
- Beyaz S, Mana M, Roper J et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. *Nature*. 2016; 531(7592):53-58. <https://doi.org/10.1038/nature17173>
- Pietrocola F, Pol J, Vacchelli E et al. Caloric Restriction Mimetics Enhance Anticancer Immunosurveillance. *Cancer Cell*. 2016; 30(1):147-160. <https://doi.org/10.1016/j.ccell.2016.05.016>
- Raffaghello L, Lee C, Safdie F et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. *Proceedings of the National Academy of Sciences*. 2008; 105(24):8215-8220. <https://doi.org/10.1073/pnas.0708100105>
- Englert J, Powell J. Hunger Pains: Stimulating the Appetite of the Immune System for Cancer. *Cancer Cell*. 2016; 30(1):13-15. <https://doi.org/10.1016/j.ccell.2016.06.019>
- Beyaz S, Mana M, Roper J et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. *Nature*. 2016; 531(7592):53-58. <https://doi.org/10.1038/nature17173>
- O'Brien L, Soliman S, Li X, Bilder D. Altered Modes of Stem Cell Division Drive Adaptive Intestinal Growth. *Cell*. 2011; 147(3):603-614. <https://doi.org/10.1016/j.cell.2011.08.048>
- Richmond C, Shah M, Deary L et al. Dormant Intestinal Stem Cells Are Regulated by PTEN and Nutritional Status. *Cell Rep*. 2015; 13(11):2403-2411. <https://doi.org/10.1016/j.celrep.2015.11.035>
- Yilmaz Ö, Katajisto P, Lamming D et al. mTORC1 in the Paneth cell niche couples intestinal stem-cell function to calorie intake. *Nature*. 2012; 486(7404):490-495. <https://doi.org/10.1038/nature11163>
- Beyaz S, Mana M, Roper J et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. *Nature*. 2016; 531(7592):53-58. <https://doi.org/10.1038/nature17173>
- Rodríguez-Colman M, Schewe M, Meerlo M et al. Interplay between metabolic identities in the intestinal crypt supports stem cell function. *Nature*. 2017; 543(7645):424-427. <https://doi.org/10.1038/nature21673>
- Iglesias M, Felix D, Gutiérrez-Gutiérrez Ó et al. Downregulation of mTOR Signaling Increases Stem Cell Population Telomere Length during Starvation of Immortal Planarians. *Stem Cell Reports*. 2019; 13(2):405-418. <https://doi.org/10.1016/j.stemcr.2019.06.005>
- Flores I, Canela A, Vera E, Tejera A, Cotsarelis G, Blasco M. The longest telomeres: a general signature of adult stem cell compartments. *Genes Dev*. 2008; 22(5):654-667. <https://doi.org/10.1101/gad.451008>
- González-Estévez C, Felix D, Smith M et al. SMG-1 and mTORC1 Act Antagonistically to Regulate Response to Injury and Growth in Planarians. *PLoS Genet*. 2012; 8(3):e1002619. <https://doi.org/10.1371/journal.pgen.1002619>
- González-Estévez C, Felix D, Rodríguez-Esteban G, Aboobaker A. Decreased neoblast progeny and increased cell death during starvation-induced planarian degrowth. *Int J Dev Biol*. 2012; 56(1-2-3):83-91. <https://doi.org/10.1387/ijdb.113452cg>
- González-Estévez C, Flores I. Fasting for stem cell rejuvenation. *Aging (Albany NY)*. 2020; 12(5):4048-4049. <https://doi.org/10.18632/aging.102912>
- Brandhorst S, Choi I, Wei M et al. A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan. *Cell Metab*. 2015; 22(1):86-99. <https://doi.org/10.1016/j.cmet.2015.05.012>
- Fadini G, Tura A, Pacini G, Avogaro A, Vigili de Kreutzenberg S. Reduced circulating stem cells associate with excess fasting and post-load NEFA exposure in healthy adults with normal glucose tolerance. *Atherosclerosis*. 2017; 261:117-123. <https://doi.org/10.1016/j.atherosclerosis.2017.03.002>