Journal of Advances in Medicine and Medical Research

31(12): 1-10, 2019; Article no.JAMMR.53852
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Undesirable Outcomes of Starvation Therapy of Cancer Require Special Attention

Fawwaz Shakir Al Joudi[1*]

[1]Biotechnology Program, Faculty of Engineering, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S 4L8, Canada.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMMR/2019/v31i1230339
Editor(s):
(1) Prof. Abrao Rapoport, General Director of Heliopolis Cancer Hospital, Sao Paulo University, Brazil.
Reviewers:
(1) Michael Bordonaro, Geisinger Commonwealth School of Medicine, USA.
(2) Amal Halim, Mansoura University, Egypt.
(3) Amira Muhammad Galal Darwish, Arid Lands Cultivation Research Institute (ALCRI) and City of Scientific Research and Technological Applications (SRTA-City), Egypt.
Complete Peer review History: http://www.sdiarticle4.com/review-history/53852

Mini-review Article

Received 15 November 2019
Accepted 20 January 2020
Published 27 January 2020

ABSTRACT

Nutritional starvation is a growing area of research into development of cancer therapy. Within the vast amount of positive research findings in starvation trials, there have been weaknesses in some of the systems utilized. Because such weaknesses are taken as adverse points that must be well-thought-out and avoided, such negative effects have been sought from the literature and presented in this work. This mini-review can then be a suitable guide for researchers and clinicians to either avoid situations where the growth of certain cancer cells is enhanced by certain forms or modes of starvation, or their metastatic abilities are boosted. The intra- and extra-cellular mechanisms associated with these cellular enhancements have been demonstrated. Some negative interactions of starvation with chemotherapy have also been included. The understanding of these mechanisms can help avoid them for better future experimental and clinical results and may, at the same time, open new avenues for research workers to find ways of dismantling them.

Keywords: Cancer; starvation therapy; cancer cells; negative outcomes; cellular mechanisms.

**Corresponding author: E-mail: fawwazaljoudi@gmail.com;*

1. INTRODUCTION

Cancer therapy by cell starvation has been the focus of many researchers and oncologists with promising knowledge accumulating over the past few decades. Workers have anticipated this to become a successful therapeutic intervention for cancer. In the course of research, a vast number of experimental starvation procedures tested have appeared in the literature [1,2]. However, the response to starvation was found to vary among various cancer cells whereby poorly differentiated and highly aggressive cells appeared to be more tolerant [3]. Moreover, and in the midst of the optimism about the effects of starvation on cancer, a number of methods used in the experimental starvation of various types of cancer failed to meet with the desired therapeutic targets and may even have induced cancer cell tolerance instead [4]. Hence, this brief communication has been prepared to give a description of the reported experiments and research protocols with negative outcomes, in addition to an account of the molecular mechanisms adopted by cancer cells to become resistant and lead to non-anticipated results. Such information may stand as guidelines for starvation research into either avoiding such protocols or finding solutions for them.

2. NEGATIVE POTENTIALS IN STARVATION THERAPY

Oncologists refrain from starving patients with malignancies, especially children, since nutrition is necessary to enhance their survival and alleviate the effects of cancer cachexia [5]. Experiments have shown that nutritional starvation may cause wasting of the body of rats with methylcholanthrene-induced sarcomas, allowing tumours to grow [6]. Other experimental examples of the adverse effects of starvation were demonstrated when KHT fibrosarcoma cells and lymphoma cells showed enhanced metastatic potentials upon induction of acidosis [7,8]. Clinically, even short-term starvation of severely debilitated patients was associated with unfavourable outcomes [9,10]. Furthermore, a reduction in the number of immunocompetent cells was described following a few days of starvation [11]. Moreover, and unlike positive anticipated effects, malignant transformation would, at times, take place following long-term starvation stress, possibly due to chromosomal instability that may yield cells with even more aggressive malignancy phenotypes [12,13]. Similarly, chemical initiation of hepatocellular carcinoma in rats was followed by an accelerated development of the tumour when put under the stress of fasting-feeding cycles [14]. From metabolism points of view, the uptake of glucose and the synthesis of macromolecules by glucose-starved Wilms' tumour cells was found to be augmented by insulin [15]. A practical example of this is the suppression of the growth of Ehrlich ascites cells in mice with induced diabetes and starved for glucose. The suppressed Ehrlich ascites cells resume growth upon insulin administration pointing out the role of insulin in sustaining the metabolism and survival of tumour cells [16]. Another well reported starvation potential that yielded unwanted results have been the adverse effects of glutamine deprivation on the growth of cancer cells [17], mainly due to compensatory utilization and synthesis of asparagine and other non-essential amino acids [18]. In some tumour types, and in the absence of extracellular glutamine, a compensatory cellular mechanism acts, whereby p53 promotes the expression of SLC1A3, promoting for a molecular pathway that enhances glutamate, glutamine, and nucleotide synthesis to rescue cell viability [19]. Similar controversies have been described, whereby the deficiency/ starvation for L-arginine may yield unexpected tumour growth, especially in patients with arginine non-auxotrophic cancer types [20]. Another enhancement of glutamine depletion can be through the use glutaminase inhibitor or transporter inhibitor [21].

3. CELLULAR MECHANISMS OF CELL SURVIVAL UNDER THE STARVATION STRESS

A number of mechanisms have been described through which some cancer cells achieve a state of resistance to starvation. Works that employed hormonal therapies were, initially, met with some failures. Androgens or cytokines starvation can enhance the proliferation of prostate cancer cells especially following their increased expression of p300 [22]. Toll-like receptor 4 (TLR-4) positive prostate cancer cells can also overcome the starvation inhibition upon lipopolysaccharide (LPS) stimulation of the TLR 4 [23]. Also, mediated by the p-53-activated p-21, serine stringency was found to enhance shifting some prostate cancer cells into glutathione production to combat reactive oxygen species [ROS] [24,25].

In a similar mode, the breast cancer cell line MCF-7/BUS can resist the apoptosis induced by

estrogen starvation through a mechanism that involves GPR-78, and the level of its expression may serve as a marker for the responsiveness of breast cancer cells to estrogen manipulation therapy [26]. Mammary epithelial tumour cells have also been reported to utilize the serum-and glucocorticoid-induced protein kinase (Sgk) to rescue their survival during episodes of serum starvation [27].

Colon cancer cells may develop resistance to glucose deprivation through a number of molecular mechanisms: The oncosuppressor protein, HIPK2 (the homeodomain-interacting protein kinase 2), the c-Jun NH2-terminal kinase activation, or through the ATM/Chk2/p53 signalling pathway [28,29]. Colon carcinoma cells can also resist thymidine deprivation [30] possibly through a mechanism that resembles the persistence of a calcium-independent melanoma cell line in spite of thymidine deprivation [31].

Starved malignant glioma cells survive through glycolysis and accelerated respiration induced by Tp53 [32,33]. Also, the recovery of the pancreatic adenocarcinoma cell line MiaPaCa2 is mediated through the defensive mechanism of the Nupr1 [34]. Similarly, the increased expression of Mcl-1, a member of the bcl-2 family, rescued immortalised mouse embryonic fibroblasts from the starvation stress [35].

Furthermore, hypoxia and glucose starvation may augment the invasiveness of the cancer cell line HepG2 cells, aided by the Akt/ARK5 system and the AMP-activated protein kinase-alpha which mediates the hypoxia-induced transforming growth factor-beta1 [36,37]. Clearly described has been the inhibition of proteasome formation in the tumourigenic breast cancer cell line, MCF-7, leading to enhanced survival as these cells appear to acquire resistance to protein breakdown [38]. Amino acid starvation of MCF-7 cells was also found to induce the expression of cd24 mRNA which may play a role in the progression of breast cancer [39]. Another intra-cellular mechanism described has been the CLIC4/mtCLIC, a chloride intracellular channel protein, which also inhibits autophagy and apoptosis upon starvation of glioma cells [40]. Under limited glucose levels, survival of cancer cells was improved by the increased expression of the purine synthesis intermediate, succinylaminoimidazolecarboxamide ribose-5' (SAICAR) and its interaction with phosphate pyruvate kinase isoform (M2PK M2) [41]. Thus, it was concluded that some cancer cells may benefit from autophagy induced by starvation since they can utilize the autophagy products as energy sources [42,43].

In addition to the intra-cellular mechanisms described above, a number of other mechanisms that maintain cancer cell survival in starvation have also been described. One mechanism that accompanied the glucose starvation stress has been the chaperone-epidermal growth complex formation that prevented the release of the epidermal growth factor receptor (EGFR) until the removal of the stress [44]. Another mechanism which enables malignant cells to survive glucose starvation and hypoxia has been the increase, persistence and selectivity of the expression of the vascular endothelial growth factor (VEGF) that maintains and induces angiogenesis [45-48]. Similarly, VEGF mRNA is up-regulated in colon carcinoma cells through various MAPK pathways which stimulate the extracellular signal-regulated kinases (Erk-1/2) [49].

Under-nutrition of HeLa cells increases glycolysis for ATP production through induction of reactive oxygen species (ROS) production and phosphorylation of AMP-activated protein kinase (AMPK) [50]. This mechanism appears to mimic the Warburg effect [51] and provides some protection to growing cancer cells. Similarly, cancer cells under starvation stress can even utilize the mucin-1 (MUC-1) oncoprotein to induce autophagy and reduce the effects of glucose deprivation-induced ROS [52]. Other tumour cells also appear to resist starvation by blocking translation elongation through a mechanism lead by the eucaryotic elongation factor 2 kinase (eEFK-2) [53,54]. Moreover, the expression of wild type p53 in some cancer cells may confer the ability to inhibit starvation-induced autophagy [55]. It may well be mentioned that arachidonic acid or nordihydroguaiaretic acid [NDGA], a lipoxygenase inhibitor can rescue W256 carcinosarcoma cells of the monocytoid origin from apoptosis due to serum starvation [56]. Also, the tumourigenic DA breast cells have been shown to over-express the marker of metastasis, Ly-6, when put under stress of serum starvation or heat shock [57].

Glucose-starved leukaemia cells can be rescued by the early addition of inhibitors of signalling or anti-oxidants [58], pointing out the effects of unnecessary use of anti-oxidants that may disrupt the oxidative-anti-oxidative homeostasis

[59]. Similarly, insulinoma cells grown under glucose and amino acid starvation conditions resisted apoptosis, probably due to increased ability to withstanding oxidative stress [60]. In addition, autophagy of hepatocellular carcinoma cells was induced by hepatitis B x antigen or by hypoxia and were relieved by nutrient starvation, an opposite beclin-1-mediated effect [61-63]. In addition, starvation of a number of human colorectal cancers and breast cancer cell lines appeared to induce the p21 inhibition, which was overcome by the anti-Bcl-2 agent, ABT-737 [64,65].

Fasting-re-feeding may enhance tumour development of colon cancer in a mitogenic fashion [66]. Furthermore, starved rats showed a potential for initiation of hepatic carcinogenesis following nitrosamine treatment, when followed by re-feeding [67]. All the above mechanisms have been summarised and displayed in Tables 1 and 2.

Table 1. The intra-cellular mechanisms that extend the survival of cancer cell lines during starvation

Cell type and effector manipulation	Mechanisms of survival	References
Androgens or cytokines starvation of prostate cancer cells	Increased expression of p300	[22]
TLR-4-positive prostate cancer cells under general energy starvation	LPS stimulation of the TLR 4	[23]
Prostate cancer cells under serine stringency	p-53-activated p21	[24,25]
Estrogen starvation-induced apoptosis breast cancer cell line [MCF-7/BUS]	GPR-78	[26]
Serum starvation of mammary epithelial tumour cells	Sgk	[27]
Amino acid starvation of MCF-7 cells	Induce the expression of cd24 mRNA which may play a role in the progression of breast cancer	[39]
Glucose deprivation of colon cancer cells	HIPK2 or the ATM/Chk2/p53 signalling pathway	[28,29]
Thymidine deprivation of colon carcinoma cells	Calcium-independent mechanism	[30,31]
Starved malignant glioma cells	Glycolysis and accelerated respiration induced by Tp53 [	[32,33]
The pancreatic adenocarcinoma cell line MiaPaCa2	The defensive mechanism of the Nupr1	[34]
Immortalised mouse embryonic fibroblasts	Increased expression of Mcl-1	[35]
Hypoxia and glucose starvation of HepG2cancer cell line	The Akt/ARK5 system and the AMP-activated protein kinase-alpha which mediates the hypoxia-induced transforming growth factor-beta1	[36,37]
The tumourigenic cell line, MCF-7	Inhibition of proteasome formation leading to enhanced survival as such cells appear to acquire resistance to protein breakdown	[38]
Starved glioma cells	The CLIC4/mtCLIC, a chloride intracellular channel protein, which also inhibits autophagy and apoptosis upon starvation	[40]
Cancer cells under limited glucose levels	Increased expression of SAICAR and its interaction with M2PK M2	[41]

Table 2. The functional and extra-cellular mechanisms that enhance the survival of cancer cells in starvation

Cell type and effector manipulation	Mechanisms of survival	References
Malignant cells to survive glucose starvation and hypoxia	VEGF that maintains and induces angiogenesis	[45-48]
Starved tumour cells	Blocking translation elongation through a mechanism lead by the eEFK-2	[53, 54]
Cancer cell starvation	Wild type p53 in may confer the ability to inhibit starvation-induced autophagy	[55]
Glucose starvation stress of human epidermoid carcinoma A431 cells	Chaperone-epidermal growth complex formation that prevented the release of the epidermal growth factor receptor [EGFR] until the removal of the stress	[44]
Colon carcinoma cells	MAPK pathways including stimulating extracellular signal-regulated kinases [Erk-1/2] that up-regulate of the VEGF mRNA	[49]
Under-nutrition of HeLa cells	Increases glycolysis for ATP production through induction of ROS production and phosphorylation of AMPK	[50]
Cancer cells under starvation stress	Utilizing the MUC-1 oncoprotein to induce autophagy and reduce the effects of glucose deprivation-induced ROS	[52]
Serum starvation of W256 carcinosarcoma cells of the monocytoid origin	Rescued by arachidonic acid or nordihydroguaiaretic acid [NDGA], a lipoxygenase inhibitor	[56]
DA breast cells	Over-express the marker of metastasis, Ly-6	[57]
Glucose-starved leukaemia cells	Early addition of inhibitors of signalling or anti-oxidants	[58]
Glucose and amino acid starvation of insulinoma cells	Increased capability to stand oxidative stress	[60]
Induced autophagy of hepatocellular carcinoma cells	Nutrient starvation, an opposite beclin-1-mediated effect	[61-63]
Nutrient starvation of human colorectal cancers and breast cancer cell lines	Induction of p21 inhibition	[64, 65]
Fasting-re-feeding of colon cancer in	A mitogenic effect or mode	[66]
Initiation of hepatic carcinogenesis following nitrosamine treatment in starved rats	A mitogenic effect or mode	[67]

4. CONVENTIONAL THERAPY AND STARVATION

It has been reported that starvation may enhance the action of conventional cancer therapies, in what has been described as the differential stress syndrome (DSS) [68,69]. Nevertheless, the susceptibilities of various types of cancer to chemotherapeutic agents under various starvation regimens were found to vary greatly [70], and resistance to chemotherapy may be mediated by the starvation-induced multiple drug resistance gene-1 ([MDR-1) [71]. Besides, some cell lines such as the KHT 35LI was found to generate variants resistant to methotraxate [72]. Moreover, glucose starvation has also been unfavourable for the cisplastin-induced apoptosis of the human epidermoid

carcinoma cell line A431 [73]. The growth of liver carcinoma cells is not suppressed by 5-fluoro-uracil during glucose starvation [74].

5. CONCLUSIONS AND RECOMMENDA-TIONS

Cancer therapy by starvation is certainly not a straight forward method that can make dramatic therapeutic responses since failures are expected in its' fight against cancer and cancer cells. Many of the reported mechanisms that prevent starvation stress-induced apoptosis or from autophagy have been described. These mechanisms must be considered in designing experimental or even clinical approaches to tumour starvation, especially that no conclusive evidence has been presented suggesting that dietary manipulations would give absolute benefit to cancer patients' general health, or cause regression of tumours [75]. Furthermore, and whenever feasible, cancer cells may be tested prior to the start of any management protocols, to unveil any existing adverse mechanisms with potential survival enhancement. The current work may provide preliminary guidelines for performing such para-clinical scientific activity, which may provide more solid bases for clinical decisions. An example of such a proposal has been the levels of GPR-78 which may serve as a marker for the responsiveness of breast cancer cells to estrogen manipulation therapy [26]. In addition, nano-clustered cascaded enzymes that release glucose oxidase can deplete the cells off glucose and oxygen [76]. Regarding the immune system, the adverse effects reported earlier have been debated recently in scientific works and even in newspaper declarations and articles emphasizing the positive effects of fasting cycles through inducing stem cells to boost the immune system [77]. For its significance, this issue has recently been taken up by the general media [78,79]. Furthermore, the cancer starvation therapy mode has been a major issue during the past years and has been extensively researched into. Yet, published information on organized clinical trials has not been made available. In the midst of the euphoria of some advances in the topic, some lines are required to be drawn to avoid unnecessary failures. Such procedures would consider early recognition of modes of cancer cell survival. Knowledge of those may allow either avoiding them, if possible, by altering the starvation procedures, or rather intervention by methods such as cellular or genetic manipulations.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Al Joudi FS. Cancer therapy by nutritional restrictions: Current knowledge and future guidelines. Br J Med Res. 2016;11(90):1-19.
2. Naveed S, Aslam M, Ahmad A. Starvation based differential chemotherapy: A novel approach for cancer treatment. Oman Med J. 2014;29(6):391-8.
3. Janeckova H, Vesely P, Chmelik R. Proving tumour cells by acute nutritional/energy deprivation as a survival threat: A task for microscopy. Anticancer Res. 2009;29(6):2339-45.
4. Caccialanza R, Aprile G, Cereda E, Pedrazzoli P. Fasting in oncology: Word of caution. Nat Rev Cancer. 2019;19(3):177. DOI: 10.1038/s41568-018-0098-0
5. Andrassy RJ, Chwals WJ. Nutritional support of the pediatric oncology patient. Nutrition. 1998;14(1):124-9.
6. Goodgame JT Jr, Lowry SF, Reilly JJ, Jones DC, Brennan MF. Nutritional manipulations and tumor growth. I. The effects of starvation. Am J Clin Nutr. 1979;32(11):2277-84.
7. Ryder CB, McColl K, Distelhorst CW. Acidosis blocks CCAAT/enhancer-binding protein homologous protein [CHOP]- and c-Jun-mediated induction of p53-upregulated mediator of apoptosis (PUMA) during amino acid starvation. Biochem Biophys Res Commun. 2013;430(4):1283-8. DOI: 10.1016/j.bbrc.2012.11.136 (Epub 2012 Dec 19)
8. Schlappack OK, Zimmermann A, Hill RP. Glucose starvation and acidosis: Effect on experimental metastatic potential, DNA content and MTX resistance of murine tumour cells. Br J Cancer. 1991;64(4):663-70.

9. Caccialanza R, De Lorenzo F, Gianotti L, Zagonel V, Gavazzi C, Farina G, et al. Nutritional support for cancer patients: Still a neglected right? Support Care Cancer. 2017;25(10):3001-3004.
DOI: 10.1007/s00520-017-3826-1
(Epub 2017 Jul 14)
10. de Groot S, Pijl H, van der Hoeven JJM, Kroep JR. Effects of short-term fasting on cancer treatment. J Exp Clin Cancer Res. 2019;38(1):209.
DOI: 10.1186/s13046-019-1189-9
11. Martinez D, Cox S, Lukassewycz OA, Murphy WH. Immune mechanisms in leukemia: Suppression of cellular immunity by starvation. J Natl Cancer Inst. 1975;55(4):935-9.
12. Tavaluc RT, Hart LS, Dicker DT, El-Deiry WS. Effects of low confluency, serum starvation and hypoxia on the side population of cancer cell lines. Cell Cycle. 2007;6(20):2554-62.
13. Zhang J, Wang X, Zhao Y, Chen B, Suo G, Dai J. Neoplastic transformation of human diploid fibroblasts after long-term serum starvation. Cancer Lett. 2006;243(1):101-8.
14. Tomasi C, Laconi E, Laconi S, Greco M, Sarma DS, Pani P. Effect of fasting/refeeding on the incidence of chemically induced hepatocellular carcinoma in the rat. Carcinogenesis. 1999;20(10):1979-83.
15. Lemmon SK, Sens DA, Buse MG. Insulin stimulation of glucose transport and metabolism in a human Wilms' tumor-derived myoblast-like cell line: Modulation of hormone effects by glucose deprivation. J Cell Physiol. 1985;125(3):456-64.
16. Fung KP, Chan TW, Choy YM. Suppression of Ehrlich ascites tumor growth in mice by starvation and streptozotocin-induced diabetes. Cancer Lett. 1985;28(3):273-80.
17. Jie Jiang, Sankalp Srivastava, Ji Zhang. Starve cancer cells of glutamine: Break the spell or make a hungry monster? Cancers. 2019;11(6):804.
Available:https://doi.org/10.3390/cancers11060804
18. Pavlova NN, Hui S, Ghergurovich JM, Fan J, Intlekofer AM, White RM, Rabinowitz JD, Thompson CB, Zhang J. As extracellular glutamine levels decline, asparagine becomes an essential amino acid. Cell Metab. 2018;27:428–438.
DOI: 10.1016/j.cmet.2018.07.005
(Epub 2018 Aug 16)
19. Tajan M, Hock AK, Blagih J, Robertson NA, Labuschagne CF, Kruiswijk F, Humpton TJ, Adams PD, Vousden KH. A role for p53 in the adaptation to glutamine starvation through the expression of SLC1A3. Cell Metab. 2018;28(5):721-736.e6.
20. Szefel J, Danielak A, Kruszewski WJ. Metabolic pathways of L-arginine and therapeutic consequences in tumors. Adv Med Sci. 2019;64(1):104-110.
DOI: 110.1016/j.advms.2018.08.018
(Epub 2018 Dec 31)
21. Fung MKL, Chan GC. Drug-induced amino acid deprivation as strategy for cancer therapy. J Hematol Oncol. 2017;10(1):144.
DOI: 10.1186/s13045-017-0509-9
22. Heemers HV, Sebo TJ, Debes JD, Regan KM, Raclaw KA, Murphy LM, et al. Androgen deprivation increases p300 expression in prostate cancer cells. Cancer Res. 2007;67(7):3422-30. Prostate.
(2015 Apr 2)
DOI: 10.1002/pros.22983
23. Jain S, Suklabaidya S, Das B, Raghav SK, Batra SK, Senapati S. TLR4 activation by lipopolysaccharide confers survival advantage to growth factor deprived prostate cancer cells. Prostate. 2015;75(10):1020-33.
DOI: 10.1002/pros.22983
(Epub 2015 Apr 2)
24. Maddocks OD, Berkers CR, Mason SM, Zheng L, Blyth K, Gottlieb E, et al. Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells. Nature. 2013;493(7433):542-6.
25. Tavana O, Gu W. The hunger games: p53 regulates metabolism upon serine starvation. Cell Metab. 2013;17(2):159-61.
26. Fu Y, Li J, Lee AS. GRP78/BiP inhibits endoplasmic reticulum BIK and protects human breast cancer cells against estrogen starvation-induced apoptosis. Cancer Res. 2007;67(8):3734-40.
27. Leong ML, Maiyar AC, Kim B, O'Keeffe BA, Firestone GL. Expression of the serum- and glucocorticoid-inducible protein kinase, Sgk, is cell survival response to multiple types of environmental stress stimuli in mammary epithelial cells. J Biol Chem. 2003;278(8):5871-82.
28. Garufi A, Ricci A, Trisciuoglio D, Iorio E, Carpinelli G, Pistritto G, et al. Glucose restriction induces cell death in parental but not in homeodomain-interacting protein

kinase 2-depleted RKO colon cancer cells: Molecular mechanisms and implications for tumor therapy. Cell Death Dis. 2013;4:e639.
DOI: 10.1038/cddis.2013.163

29. Shi Y, Felley-Bosco E, Marti TM, Orlowski K, Pruschy M, Stahel RA. Starvation-induced activation of ATM/Chk2/p53 signaling sensitizes cancer cells to cisplatin. BMC Cancer. 2012;12:571.
DOI: 10.1186/1471-2407-12-571
30. Harwood FG, Frazier MW, Krajewski S, Reed JC, Houghton JA. Acute and delayed apoptosis induced by thymidine deprivation correlates with expression of p53 and p53-regulated genes in colon carcinoma cells. Oncogene. 1996;12(10):2057-67.
31. Parsons PG, Musk P, Goss PD, Leah J. Effects of calcium depletion on human cells *in vitro* and the anomalous behavior of the human melanoma cell line MM170. Cancer Res. 1983;43(5):2081-7.
32. Steinbach JP, Wolburg H, Klumpp A, Probst H, Weller M. Hypoxia-induced cell death in human malignant glioma cells: Energy deprivation promotes decoupling of mitochondrial cytochrome c release from caspase processing and necrotic cell death. Cell Death Differ. 2003;10(7):823-32.
33. Wanka C, Steinbach JP, Rieger. Tp53-induced glycolysis and apoptosis regulator [TIGAR] protects glioma cells from starvation-induced cell death by up-regulating respiration and improving cellular redox homeostasis. J Biol Chem. 2012;287(40):33436-46.
34. Hamidi T, Cano CE, Grasso D, Garcia MN, Sandi MJ, Calvo EL, et al. Nupr1-aurora kinase A pathway provides protection against metabolic stress-mediated autophagic-associated cell death. Clin Cancer Res. 2012;18(19):5234-46.
35. Austin M, Cook SJ. Increased expression of Mcl-1 is required for protection against serum starvation in phosphatase and tensin homologue on chromosome 10 null mouse embryonic fibroblasts, but repression of Bim is favored in human glioblastomas. J Biol Chem. 2005;280(39): 33280-8.
36. Cuvier C, Jang A, Hill RP. Exposure to hypoxia, glucose starvation and acidosis: Effect on invasive capacity of murine tumor cells and correlation with cathepsin [L + B] secretion. Clin Exp Metastasis. 1997;15(1): 19-25.
37. Suzuki A, Kusakai G, Shimojo Y, Chen J, Ogura T, Kobayashi M, et al. Involvement of transforming growth factor-beta 1 signaling in hypoxia-induced tolerance to glucose starvation. J Biol Chem. 2005;280(36):31557-63.
(Epub 2005 Jul 13)
38. Mizrachy-Schwartz S, Cohen N, Klein S, Kravchenko-Balasha N, Levitzki A. Amino acid starvation sensitizes cancer cells to proteasome inhibition. IUBMB Life. 2010;62(10):757-63.
39. Liu W, Vadgama JV. Identification and characterization of amino acid starvation-induced CD24 gene in MCF-7 human breast cancer cells. Int J Oncol. 2000;16(5):1049-54.
40. Zhong J, Kong X, Zhang H, Yu C, Xu Y, Kang J, et al. Inhibition of CLIC4 enhances autophagy and triggers mitochondrial and ER stress-induced apoptosis in human glioma U251 cells under starvation. PLoS One. 2012;7(6):e39378.
DOI: 10.1371/journal.pone.0039378
(Epub 2012 Jun 25)
41. Keller KE, Tan IS, Lee YS. SAICAR stimulates pyruvate kinase isoform M2 and promotes cancer cell survival in glucose-limited conditions. Science. 2012; 338(6110):1069-72.
42. Rabinowitz JD, White E. Autophagy and metabolism. Science. 2010;330(6009): 1344-8.
43. Poillet-Perez L, White E. Role of tumor and host autophagy in cancer metabolism. Genes Dev. 2019;33(11-12):610-619.
DOI: 10.1101/gad.325514.119
44. Cai B, Tomida A, Mikami K, Nagata K, Tsuruo T. Down-regulation of epidermal growth factor receptor-signaling pathway by binding of GRP78/BiP to the receptor under glucose-starved stress conditions. J Cell Physiol. 1998;177(2):282-8.
45. Shweiki D, Neeman M, Itin A, Keshet E. Induction of vascular endothelial growth factor expression by hypoxia and by glucose deficiency in multicell spheroids: Implications for tumor angiogenesis. Proc Natl Acad Sci USA. 1995;92(3):768-72.
46. Vintonenko N, Pelaez-Garavito I, Buteau-Lozano H, Toullec A, Lidereau R, Perre GY, et al. Overexpression of VEGF189 in breast cancer cells induces apoptosis via NRP1 under stress conditions. Cell Adh Migr. 2011;5(4):332-43.
47. Yamamoto N, Mammadova G, Song RX, Fukami Y, Sato K. Tyrosine

phosphorylation of p145met mediated by EGFR and Src is required for serum-independent survival of human bladder carcinoma cells. J Cell Sci. 2006;119(Pt 22): 4623-33.

48. Zhang L, Conejo-Garcia JR, Yang N, Huang W, Mohamed-Hadley A, Yao W, et al. Different effects of glucose starvation on expression and stability of VEGF mRNA isoforms in murine ovarian cancer cells. Biochem Biophys Res Commun. 2002;292(4):860-8.
49. Jung YD, Nakano K, Liu W, Gallick GE, Ellis LM. Extracellular signal-regulated kinase activation is required for up-regulation of vascular endothelial growth factor by serum starvation in human colon carcinoma cells. Cancer Res. 1999;59(19): 4804-7.
50. Wu CA, Chao Y, Shiah SG, Lin WW. Nutrient deprivation induces the Warburg effect through ROS/AMPK-dependent activation of pyruvate dehydrogenase kinase. Biochim Biophys Acta. 2013;1833(5):1147-56.
51. Warburg O. On the origin of cancer cells. Science, New Series. 1956;123(3191):309-14.
52. Yin L, Kharbanda S, Kufe D. MUC1 oncoprotein promotes autophagy in a survival response to glucose deprivation. Int J Oncol. 2009;34(6):1691-9.
53. Leprivier G, Remke M, Rotblat B, Dubuc A, Mateo AR, Kool M, et al. The eEF2 kinase confers resistance to nutrient deprivation by blocking translation elongation. Cell. 2013;153(5):1064-79.
54. Manning BD. Adaptation to starvation: Translating a matter of life or death. Cancer Cell. 2013;23(6):713-5.
55. Scherz-Shouval R, Weidberg H, Gonen C, Wilder S, Elazar Z, Oren M. p53-dependent regulation of autophagy protein LC3 supports cancer cell survival under prolonged starvation. Proc Natl Acad Sci USA. 2010;107(43):18511-6.
56. Tang DG, Guan KL, Li L, Honn KV, Chen YQ, Rice RL, et al. Suppression of W256 carcinosarcoma cell apoptosis by arachidonic acid and other polyunsaturated fatty acids. Int J Cancer. 1997;72(6):1078-87.
57. Treister A, Sagi-Assif O, Meer M, Smorodinsky NI, Anavi R, Golan I, et al. Expression of Ly-6, a marker for highly malignant murine tumor cells, is regulated by growth conditions and stress. Int J Cancer. 1998;77(2):306-13.
58. Mendivil-Perez M, Jimenez-Del-Rio M, Velez-Pardo C. Glucose starvation induces apoptosis in a model of acute T leukemia dependent on caspase-3 and apoptosis-inducing factor: A therapeutic strategy. Nutr Cancer. 2013;65(1):99-109.
59. Al Joudi FS. Adverse effects of antioxidant supplements and their underlying mechanisms. Aging Res and Clin Practice. 2013;2(4):339-345.
60. Olejnicka BT, Dalen H, Baranowski MM, Brunk UT. Starvation-induced auto-phagocytosis paradoxically decreases the susceptibility to oxidative stress of the extremely oxidative stress-sensitive NIT insulinoma cells. Redox Rep. 1997;3(5-6): 311-8.
61. Gou X, Ru Q, Zhang H, Chen Y, Li L, Yang H, et al. HAb18G/CD147 inhibits starvation-induced autophagy in human hepatoma cell SMMC7721 with an involvement of Beclin 1 down-regulation. Cancer Sci. 2009;100(5):837-43.
62. Song J, Guo X, Xie X, Zhao X, Li D, Deng W, et al. Autophagy in hypoxia protects cancer cells against apoptosis induced by nutrient deprivation through a Beclin1-dependent way in hepatocellular carcinoma. J Cell Biochem. 2011;112(11): 3406-20.
63. Tang H, Da L, Mao Y, Li Y, Li D, Xu Z, et al. Hepatitis B virus X protein sensitizes cells to starvation-induced autophagy via up-regulation of beclin 1 expression. Hepatology. 2009;49(1):60-71.
64. Braun F, Bertin-Ciftci J, Gallouet AS, Millour J, Juin P. Serum-nutrient starvation induces cell death mediated by Bax and Puma that is counteracted by p21 and unmasked by Bcl-x(L) inhibition. PLoS One. 2011;6(8):e23577.
DOI: 10.1371/journal.pone.0023577
(Epub 2011 Aug 24)
65. Trudel S, Stewart AK, Li Z, Shu Y, Liang SB, Trieu Y, et al. The Bcl-2 family protein inhibitor, ABT-737, has substantial antimyeloma activity and shows synergistic effect with dexamethasone and melphalan. Clin Cancer Res. 2007;13(2 Pt 1):621-9.
66. Premoselli F, Sesca E, Binasco V, Caderni G, Tessitore L. Fasting/re-feeding before initiation enhances the growth of aberrant crypt foci induced by azoxymethane in rat colon and rectum. Int J Cancer. 1998;77(2):286-94.

67. Tessitore L. Apoptosis and cell proliferation are involved in the initiation of liver carcinogenesis by a subnecrogenic dose of diethylnitrosamine in refed rats. J Nutr. 2000;130(1):104-10.
68. Mathews EH. Short-term starvation for cancer control in humans. Experimental Gerontol. 2013;48:1293.
69. Raffaghello L, Safdie F, Bianchi G, Dorff T, Fontana L, Longo VD. Fasting and differential chemotherapy protection in patients. Cell Cycle. 2010;9(22):4474-6.
70. Brandhorst S, Wei M, Hwang S, Morgan TE, Longo VD. Short-term calorie and protein restriction provide partial protection from chemotoxicity but do not delay glioma progression. Exp Gerontol. 2013;48(10): 1120-8.
71. Tanimura H, Kohno K, Sato S, Uchiumi T, Miyazaki M, Kobayashi M, et al. The human multidrug resistance 1 promoter has an element that responds to serum starvation. Biochem Biophys Res Commun. 1992;183 (2):917-24.
72. Cillo C, Ling V, Hill RP. Drug resistance in KHT fibrosarcoma cell lines with different metastatic ability. Int J Cancer. 1989;43(1): 107-11.
73. Mese H, Sasaki A, Nakayama S, Yokoyama S, Sawada S, Ishikawa T, et al. Analysis of cellular sensitization with cisplatin-induced apoptosis by glucose-starved stress in cisplatin-sensitive and -resistant A431 cell line. Anticancer Res. 2001;21(2A):1029-33.
74. Roos G, Stenram U. Relation between the incorporation of 5-fluorouracil into liver carcinoma and normal tissue RNA at hepatic arterial administration in the rat is altered by overnight starvation. J Surg Oncol. 1993;53(4):231-4.
75. Torosian MH, Daly JM. Nutritional support in the cancer-bearing host. Effects on host and tumor. Cancer. 1986;58(8 Suppl): 1915-29.
76. Ma Y, Zhao Y, Bejjanki NK, Tang X, Jiang W, Dou J, Khan MI, Wang Q, Xia J, Liu H, You YZ, Zhang G, Wang Y, Wang J. Nanoclustered cascaded enzymes for targeted tumor starvation and deoxygenation-activated chemotherapy without systemic toxicity. ACS Nano. 2019;13(8):8890-8902.
DOI: 10.1021/acsnano.9b02466
(Epub 2019 Jul 15)
77. Cheng CW, Adams GB, Perin L, Wei M, Zhou X, Lam BS, et al. Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regenera-tion and reverse immunosuppression. Cell Stem Cell. 2014;14(6):810-23.
DOI: 10.1016/j.stem.2014.04.014
78. Sarah Knapton. The Daily Telegraph, 5th June, fasting for three days can regenerate entire immune system, study finds; 2014.
79. Suzan Wu. 5th June, USC news; 2014.
Available:https://news.usc.edu/63669/fasting-triggers-stem-cell-regeneration-of-damaged-old-immune-system/

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/53852