Minireview Article

Undesirable Outcomes of Starvation Therapy of Cancer Require Special Attention

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 considered and avoided, these negative effects have been sought from the literature and presented in this work. This can then be a suitable guide for researchers and clinicians to either avoid situations where the growth of certain cancer cells can be enhanced by certain forms or modes of starvation, or their metastatic abilities be 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 mechanism can help avoid them for better clinical results and can open new avenues for research workers to find ways of dismantling them.

Key words. Cancer, starvation therapy, cancer cells, negative outcomes, cellular mechanisms.

Introduction. Cancer therapy by cell starvation has been the focus of many researchers and oncologists with promising knowledge accumulating over the past few decades, with anticipation for it to become part of research leading to successful therapeutic intervention. 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], and in the midst of the optimism of 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. Hence, this brief communication has been prepared to give a comprehensive description of the reported experiments and research protocols with negative outcomes, in addition to an account of the molecular mechanisms adopted by cancer cells that render them tolerant or lead to non-anticipated results. Such information may stand as guidelines for starvation research into either avoiding such protocols or finding solutions for them.

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 [4]. Experiments have shown that nutritional starvation may cause wasting of the body of rats with methylcholanthrene-induced sarcomas, allowing tumours to grow [5]. Other experimental examples of the adverse effects of starvation were demonstrated when KHT fibrosarcoma cells and lymphoma cells had enhanced metastatic potentials upon induction of acidosis [6-7]. Furthermore, a reduction in the number of immunocompetent cells was described following a few days of starvation [8]. Moreover, and unlike the 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 malignant phenotypes [9-10]. Hence, chemical initiation of hepatocellular carcinoma in rats was followed by accelerated development of the tumour when put under the stress of fasting-feeding cycles [11]. From metabolism points, the uptake of glucose and the synthesis of macromolecules by glucose-starved Wilms' tumour cells is augmented by insulin [12]. 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 [13]. Another well reported starvation potential that yielded unwanted results have been the adverse effects of glutamine deprivation on the growth of cancer cells [14], mainly due to compensatory utilization and synthesis of asparagine and other non-essential amino acids [15]. In some tumour types, p53 promotes the expression of SLC1A3, which enhances glutamate, glutamine, and nucleotide synthesis to rescue cell viability, in the absence of extraellular glutamine [16]. Similar controversies have been described, whereby the deficiency/ starvation for L-arginine may yield unexpected tumour growth, especially in patients with patients with arginine non-auxotrophic cancer types and those with the ability [17]. Another enhancement of glutamine depletion can be through the use glutaminase inhibitor or transporter inhibitor [18].

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 [19]. Toll-like receptor 4 (TLR-4) positive prostate cancer cells can also overcome the starvation inhibition upon lipopolysaccharide (LPS) stimulation of the TLR 4 [20]. Also, mediated by the p-53-activated p21, serine stringency enhances the shifting of some prostate cancer cells into glutathione production to combat reactive oxygen species [ROS] [21-22].

In a similar mode, the breast cancer cell line MCF-7/BUS can resist estrogen starvation-induced apoptosis 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 [23]. Mammary epithelial tumour cells have also been reported to use the serum-and glucocorticoid-induced protein kinase (Sgk) to rescue their survival during episodes of serum starvation [24]. Colon cancer cells may develop resistance to glucose deprivation through the oncosuppressor protein, the homeodomain-interacting protein kinase 2 (HIPK2), the c-Jun NH2-terminal kinase activation or through the ATM/Chk2/p53 signalling pathway [25-26]. Colon carcinoma cells can also resist thymidine deprivation [27] possibly through a mechanism that resembles the persistence of a calcium-independent melanoma cell line in spite of thymidine deprivation [28]. Starved malignant glioma cells survive through glycolysis and accelerated respiration induced by Tp53 [29-30], and the recovery of the pancreatic adenocarcinoma cell line MiaPaCa2 is mediated through the defensive mechanism of the Nupr1 [31]. Similarly, the increased expression of cl-1, a member of the bcl-2 family rescued immortalised mouse embryonic fibroblasts from the starvation stress [32].

It has been reported that 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 [33-34]. Clearly described has been the inhibition of proteasome formation in the tumourigenic cell line, MCF-7, leading to enhanced survival as such cells appear to acquire resistance to protein breakdown [35]. 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 [36]. 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 [37]. 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) [38]. 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 [39-40].

In addition to the few intra-cellular mechanisms mentioned 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 [41]. 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 [42-45]. Similarly, colon carcinoma cells utilize various MAPK pathways including stimulating extracellular signal-regulated kinases (Erk-1/2) that up-regulate of the VEGF mRNA [46].

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) [41]. This mechanism appears to mimic the Warburg effect [48] and provides some protection to growing cancer cells. And 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 [49]. Tumour cells also appear to resist starvation by blocking translation elongation through a mechanism lead by the eucaryotic elongation factor 2 kinase (eEFK-2) [50-51]. Moreover, the expression of wild type p53 in some cancer cells may confer the ability to inhibit starvation-induced autophagy [52]. 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 [53]. 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 [54].

Glucose-starved leukaemia cells can be rescued by the early addition of inhibitors of signalling or anti-oxidants [55], emphasizing the effects of unnecessary use of anti-oxidants that may disrupt the oxidative-anti-oxidative homeostasis [56]. Similarly, insulinoma cells grown under glucose and amino acid starvation conditions resisted apoptosis, probably due to increased capability to stand oxidative stress [57]. In addition, autophagy of hepatocellular carcinoma cells was induced by hepatitis B x antigen or hypoxia and were relieved by nutrient starvation, an opposite beclin-1-mediated effect [58-60]. 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 [61-62].

Fasting-re-feeding may enhance tumour development of colon cancer in a mitogenic fashion [63]. Furthermore, starved rats showed a potential for initiation of hepatic carcinogenesis following nitrosamine treatment, when followed by re-feeding [64]. All the above mechanisms have been summarised and displayed in tables 1 and 2.

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) [65-66]. Nevertheless, the susceptibilities of various types of cancer to chemotherapeutic agents under various starvation regimens were found to vary greatly [67], and resistance to chemotherapy may be mediated by the starvation-induced multiple drug resistance gene-1 ([MDR-1) [68], or that some cell lines such as the KHT 35LI can generate variants resistant to methotraxate [69]. Glucose starvation has also not been favourable for cisplastininduced apoptosis of the human epidermoid carcinoma cell line A431 [70]. The growth of liver carcinoma cells is not suppressed by 5-fluoro-uracil during glucose starvation [71].

Discussion.

Cancer therapy by starvation is certainly not a straight forward method that can make the impossible since failures are expected in its’ fight against cancer and cancer cells. Mechanisms that prevent starvation stress-induced apoptosis or from autophagy are being reported. 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 [72]. Furthermore, and whenever feasible, cancer cells can be tested prior to the start of any management protocols, to unveil any existing adverse mechanisms with potential survival enhancement. 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 [23]. In addition, nano-clustered cascaded enzymes that release glucose oxidase to deplete the cells off glucose and oxygen [73]. 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 [74]. For its significance, this issue has recently been taken up by the general media [75-76].

In conclusion, the cancer starvation therapy mode has been a major issue during the past years and has been extensively researched into, although published organized clinical trials have 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.

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	19
TLR-4-positive prostate cancer cells under general energy starvation	LPS stimulation of the TLR 4	20
prostate cancer cells under serine stringency	p-53-activated p21	21, 22
Estrogen starvation-induced apoptosis breast cancer cell line [MCF-7/BUS]	GPR-78	23
Serum starvation of mammary epithelial tumour cells	Sgk	24
Amino acid starvation of MCF-7 cells	induce the expression of cd24 mRNA which may play a role in the progression of breast cancer	36
glucose deprivation of colon cancer cells	HIPK2 or the ATM/Chk2/p53 signalling pathway	25, 26
thymidine deprivation of colon carcinoma cells	calcium-independent mechanism	27, 28
Starved malignant glioma cells	glycolysis and accelerated respiration induced by Tp53 [	29, 30
the pancreatic adenocarcinoma cell line MiaPaCa2	the defensive mechanism of the Nupr1	31
immortalised mouse embryonic fibroblasts	increased expression of cl-1	32
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	33, 34

The tumourigenic cell line, MCF-7	inhibition of proteasome formation leading to enhanced survival as such cells appear to acquire resistance to protein breakdown	35
Starved glioma cells	the CLIC4/mtCLIC, a chloride intracellular channel protein, which also inhibits autophagy and apoptosis upon starvation	37
Cancer cells under limited glucose levels	increased expression of SAICAR and its interaction with M2PK M2	38

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	42-45
Starved tumour cells	blocking translation elongation through a mechanism lead by the eEFK-2	50, 51
Cancer cell starvation	wild type p53 in may confer the ability to inhibit starvation-induced autophagy	52
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	41
colon carcinoma cells	MAPK pathways including stimulating extracellular signal-regulated kinases [Erk-1/2] that up-regulate of the VEGF mRNA	46
Under-nutrition of HeLa cells	increases glycolysis for ATP production through induction of ROS production and phosphorylation of AMPK	47
cancer cells under starvation stress	utilizing the MUC-1 oncoprotein to induce autophagy and reduce the effects of glucose deprivation-induced ROS	49
serum starvation of W256 carcinosarcoma cells of the monocytoid origin	Rescued by arachidonic acid or nordihydroguaiaretic acid [NDGA], a lipoxygenase inhibitor	53
DA breast cells	over-express the marker of metastasis, Ly-6	54
Glucose-starved leukaemia cells	early addition of inhibitors of signalling or anti-oxidants	55

glucose and amino acid starvation of insulinoma cells	increased capability to stand oxidative stress	57
Induced autophagy of hepatocellular carcinoma cells	Nutrient starvation, an opposite beclin-1-mediated effect	58-60
Nutrient starvation of human colorectal cancers and breast cancer cell lines	Induction of p21 inhibition	61, 62
Fasting-re-feeding of colon cancer in	A mitogenic effect or mode	63
initiation of hepatic carcinogenesis following nitrosamine treatment in starved rats	A mitogenic effect or mode	64

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