Opinion paper

Toward a cancer-specific diet

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A R T I C L E   I N F O

S U M M A R Y

Background & aims: It is widely acknowledged that the energy metabolism of cancer cells mainly relies on anaerobic glycolysis and this has prompted many researchers to try to reduce the malignant cells growth of experimental tumours through a programme of calorie restriction. Recently this approach has been proposed also to cancer patients. In the meantime it was demonstrated that the effects of calorie restriction on tumour growth are mediated through the toxic effect of ketone bodies on cancer cells which have a defective mitochondrial function, while these substrates are well-utilized by the normal cells.
Methods: This review analyzes the main available data regarding the tumour growth in patients undergoing a period of starvation or of normal/artificial nutrition as well as the recent approach through special normocaloric ketogenic diets which are well utilized by cancer patients while may be unfavourable for cancer cells.
Results: Despite the paucity of data it appears that modulation of tumour growth by the calorie restriction/nutritional support is unlikely in humans for several reasons: the different tumour cells growth rate and different tumour/host carcass ratio and duration of treatment, between tumour-bearing animals and patients.
Conclusion: There is a large consensus in literature that maintaining a normal body weight and preserving the lean body mass through an adequate nutrition is beneficial in cancer patients. The nutritional approach through a ketogenic diet which may be toxic for the cancer cells while is well utilized and tolerated by the patient seems promising in a next future.

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Although the first report on the clinical use of nutritional support in cancer patients dates back to 1971 [1] and enteral and parenteral nutrition are now widely recognized as belonging to the armamentarium of the modern oncologic therapy [2], there is still much uncertainty whether it is possible to design a cancer-specific nutritional regimen relying on the metabolic differences between cancer cell and host's tissues. Moreover, recently, a potential new role of the nutrition in cancer patients has evolved and concerns the potential benefits of a period of fasting in cancer patients undergoing radiation therapy or chemotherapy.

In the attempt to clarify these issues we have analysed main literature on this topic with a special focus on the experience on humans. Several different controversial points will be considered and namely: the energy requirements of the cancer cells versus the normal cells, the effects of the calorie restriction on tumour and normal cells metabolism and growth, the effects of a ketogenic

regimen on tumour growth and host metabolism and finally the clinical experience with calorie restriction and ketogenic diet in cancer patients. Since the literature on these topics is very wide, we paid particular attention during the scrutiny of the publications to two points: a) to emphasize scientific contributions on experimental models with human cancer cells or, better, on tumour-bearing patients and b) to consider the issue on the perspective of a potential translation of the research's findings into the clinical practice and hence in the respect of the human physiologic requirements of the nutrients. Finally we did not consider the possible carcinogenetic role of some nutrients (as available by many epidemiologic studies), but then we focused on the potential metabolic interaction nutrient-tumour-host in patients with a malignancy.

1. Energy requirements of the cancer and the normal cells

In 1924 the Nobel Prize winner Otto Warburg [3] discovered that cancer cells are able to produce adenosine triphosphate

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(ATP) by a high rate of anaerobic respiration, or glycolysis, which takes place in the cytosol and serves to shuffle phosphometabolites into the pentose phosphate pathway for biosynthesis of nucleic acids and lipids. This process of producing energy mainly by the non-oxidative breakdown of glucose is acknowledged as the Warburg Effect and requires a sufficient source of glucose since glucose and not oxygen (as in the healthy human karyocytes) is used to produce ATP during glycolysis. This fermentation of glucose to lactate occurs even under sufficient oxygen supply. For this purpose, cancer cells have both a remarkable up-regulation of glucose transporter molecules on their surface (the insulin-independent glucose transporter-1 and hexokinase) [4–8] and, frequently, an over-expression of several key enzymes of glycolysis and attached pathways [9,10]. This is consequent to an altered signal transduction pathways which have been recently identified. Mutations in the RAS–MAPK–ERK and PI3K–Akt–mTOR pathways and SRC may induce higher glucose uptake through the modulation of glucose transporter expression and translocation [11–13]. Moreover Akt can also promote the activity of hexokinase 1 and phosphofructokinase, enzymes involved in the production of glycolytic intermediates [14–16]. Furthermore, overexpression of some transcription factors as MYC and HIFα is regulated by PI3K–Akt–mTOR and may affect the expression of several genes associated with glycolysis [14] which include some glucose transporters and specific enzymes promoting the aerobic glycolysis phenotype, such as PKM2 and PDK1 [17–19]. Several studies of the energy metabolism in vivo in patients with sarcoma and carcinoma have also confirmed that the energy metabolism of cancer cells predominantly relies on glucose, with fat-derived calories making no appreciable contribution [20–24]. According to Holm et al. [24] the glucose net uptake by the tumour exceeds peripheral glucose uptake by a factor of 30 with a lactate output from the tumour 43 times greater than peripheral release. The glutamine consumption is highly variable [24] and in colon cancer may be similar to the tumour-free colon [25]. However, in some tumours, glutamine transport and metabolism may be upregulated and recent studies would suggest that oncogenic levels of Myc induce a transcriptional program that promotes glutaminolysis and triggers cellular addiction to glutamine as a bioenergetic substrate [26]. Mitochondrial utilization of glutamine begins with its conversion to α ketoglutarate by glutaminase and glutamate dehydrogenase. Then α-ketoglutarate can undergo to oxidation through the α-ketoglutarate dehydrogenase to succinate (standard tricarboxylic acid cycle reaction) or to a reductive carboxylation by isocitrate dehydrogenase to isocitrate and then to citrate (reverse tricarboxylic acid cycle activity). Then the glutamine-derived citrate can be transported to cytoplasm to generate acetyl CoA for anabolic processes. This may represent an alternative to glucose metabolism, especially in tumours which exhibit low glycolytic activity [27] or, may simply be a strategy of cancer cells to produce the energy required for a continuous growth.

Hence the concept that most of tumours must rely on glucose as their major energy source is now well acknowledged in the scientific community [28–30]. This metabolic reliance on glucose is the mechanism with which positive emission tomographic scans measure tumour metabolism in vivo by quantifying 18-F-2-fluoro-2-deoxyglucose uptake. It has also been possible to determine for some tumours the excess of glucose uptake as referred to the organ of origin: for instance the glucose uptake (g/d/100 g tumour) was measured to be for colon cancer 8.2 (X 4.3 cancer-free colon), for lung cancer 4.1 (X 6.7 cancer-free lung) [23,31].

2. Calorie restriction: effects on tumour and normal cells metabolism and impact on tumour growth

In 1914, Payton Rous [32] was the first to suggest that restricted food intake decreased tumour growth by reducing the tumor blood supply. These findings were subsequently replicated in the studies on experimental brain [33–36], prostate and breast tumours [37–40]. Mechanisms, however, for this biologic response and differential behaviour of normal cells, are only partially understood.

During a period of calorie restriction (CR) serum glucose and insulin levels drop down, lipolysis increases and finally leads to fatty acid-mediated activation of peroxisome proliferator-activated receptor-α (PPARα) [41]. This inhibits both the glycolysis and fatty acid synthesis and stimulates the transcription of enzymes that promote ketogenesis and mitochondrial and peroxisomal fatty acid oxidation [42]. Animal studies have revealed that increasing serum ketone levels above 1 mmol/L through carbohydrate deprivation of 50 g/day or less increases expression of monocarboxylic acid transporters in brain cells [43], leading to the substantial transfer of ketones across the blood brain barrier for energy consumption [44].

However the metabolic response to CR is different in normal and in cancer cells. In normal cells, abundant acetyl-CoA from the breakdown of ketone bodies (acetoacetate, β-hydroxybutyrate) and fatty acids due to starvation inhibits glycolysis to ensure stable ATP levels and subsequent oxidation of ketone bodies in peripheral tissue decreases the NADP+/NADPH ratio and hence increases the amount of reduced gluthathione available for scavenging H_2O_2 [45]. In the tumour cells that lack the necessary enzymes to metabolize the ketone bodies [46–49], the drop in glycolytic ATP production cannot be compensated by oxidative phosphorylation and this leads to ATP depletion and cell growth inhibition [50] and death [51–53]. There is also evidence that due to dysfunctional mitochondrial electron transport chains, many cancer cells possess high steady state levels of reactive oxygen species (ROS) that quickly leads to cell death once glycolysis is impaired [54,55]. Main mechanisms metabolic of response to fasting are depicted in Fig. 1.

Recent research has elucidated some of the molecular mediators which trigger such biochemical response. As a result of lower circulating glucose, lower insulin levels increases transcription of IGF binding protein (IGFBP)-1 and consequently decreases the bioavailability of IGF-1 [56]. Insulin and free IGF-1, through their binding to the specific tyrosine kinase receptors, activate the phosphatidylinositol-3 kinase (PI3K)–Akt–mammalian target of rapamycin complex 1 (mTORC1) pathways which promote proliferative signaling, resisting cell death and altered cellular metabolism including increased fermentation of glucose and glutamine [57]. CR activates Nrf-2 gene [58], an energy sensing network consisting of 5′ adenosine monophosphate-activated protein kinase AMPK, NAD-dependent deacetylase sirtuin-1 (SIRT1) [59], peroxisome proliferator-activated receptor-α and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) that counteract the insulin/IGF-1–PI3K–Akt–mTORC1 pathway and promote mitochondrial function.

Recently, a fasting-based intervention proved to be capable of protecting normal cells while leaving cancer cells vulnerable to high-dose chemotherapy, both in cell cultures and in neuroblastoma-bearing mice [60–63]. When in a neuroblastoma xenograft model, mice were allowed to consume only water for 48 h prior to chemotherapy, high dose etoposide led to 50% mortality in (control) fed mice, while fasting protected against the chemotoxicity normal tissues and did not compromise the killing of neuroblastoma cells.

In mammals, the mechanism responsible for the protective effect of fasting against chemotherapy induced-toxic side effects may involve reduction in the above-mentioned anabolic and mitogenic