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REVIEW

Dietary restriction: could it be considered as speed bump on tumor progression road?

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Abstract Dietary restrictions, including fasting (or long-term starvation), calorie restriction (CR), and short-term starvation (STS), are considered a strong rationale that may protect against various diseases, including age-related diseases and cancer. Among dietary approaches, STS, in which food is not consumed during designed fasting periods but is typically not restricted during designated feeding periods, seems to be more suitable, because other dietary regimens involving prolonged fasting periods could worsen the health conditions of cancer patients, being they already naturally prone to weight loss. Until now, the limited amount of available data does not point to a single gene, pathway, or molecular mechanism underlying the benefits to the different dietary approaches. It is well known that the healthy effect is mediated in part by the reduction of nutrient-related pathways. The calorie restriction and starvation (long- and short-term) also suppress the inflammatory response reducing the expression, for example, of IL-10 and TNF-α, mitigating pro-inflammatory gene expression and increasing anti-inflammatory gene expression. The dietary restriction may regulate both genes involved in cellular proliferation and factors associated to apoptosis in normal and cancer cells. Finally, dietary restriction is an important tool that may influence the response to chemotherapy in preclinical models. However, further data are needed to correlate dietary approaches with chemotherapeutic treatments in human models. The aim of this review is to discuss the effects of various dietary approaches on the cancer progression and therapy response, mainly in preclinical models, describing some signaling pathways involved in these processes.

Keywords Cancer cells · Cellular stress response · Chemotherapy · Diet · Fasting · Short-term starvation

Introduction

"Let food be thy medicine and medicine be thy food." This sentence of Hippocrates explains excellently the importance that feeding assumes in the establishment of a healthy life. In particular, various dietary approaches, such as calorie restriction and long- and short-term starvations, seem to be involved in the protection from aging and age-related diseases.

Fasting (or long-term starvation) is commonly defined as a prolonged deprivation of nutrients from a system that can be represented by cells in culture (normal or immortalized) or by multicellular organisms (from fruit flies to humans). In vitro serum deprivation, for example, is often considered as a routine procedure to reduce basal cellular activity [1] and to make the population homogeneous of proliferating cells that, in this condition, can enter in the quiescent G_0/G_1 phase [2]. Its utility includes the metabolic research in which the establishment of serum starvation-based protocols submits the physiological response to a hormonal change [3]. Moreover, other researchers have used serum starvation as a system to analyze molecular mechanisms involved in cellular stress response [4], apoptosis, and autophagy [5, 6]. That is why serum starvation has also been referred to as "environmental stress" [7] and "apoptotic trigger" [8]. Recently, starvation is assuming a

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part of protagonist. In particular, it has been spreading the idea that fasting cycles can prevent the onset of age-related diseases [9] and to improve the response to certain therapies like the oncological ones [10].

Like fasting, the reduction in calorie intake or calorie restriction (CR), without malnutrition, has been indicated as a strong non-genetic intervention that, simultaneously, can protect against various diseases, like diabetes and cancer, and that can increase the life-span in mammalians [11]. CR can consist of feeding once daily or thrice weekly over a range of restricted food amounts [12]. Also, it seems to cause a large number of benefits by reducing cardiovascular risk factors [13], improving insulin sensitivity [14], enhancing mitochondrial function (also inducing the generation of new mitochondria) [15], increasing cellular quality control through autophagy [16, 17], and reducing oxidative damage in both DNA and RNA [18].

The above considerations demonstrate that fasting or CR could be applied to protect patients from toxic side effects of chemotherapy. However, in vivo preclinical studies showed that several months may be necessary for people under CR to reach a protected state and, accordingly, these two types of approaches are not feasible for patients already prone to weight loss because of cancer itself or chemotherapy [19].

In this regard, another dietary approach that could generate similar biological changes, such as fasting and calorie restriction, seems to be more suitable. Short-term starvation (STS or intermittent fasting) is considered as a limited exposure to several nutrients, in which food is not consumed during designed fasting periods but is typically not restricted during designated feeding periods [11]. Other authors indicated it as the period of time in which animals lose weight after initiation of food restriction but prior to rebound or weight maintenance [20]. Accumulating evidence suggests that STS can produce, like CR, similar beneficial biological effects, including modulation of reactive oxygen species (ROS) and inflammatory cytokines, and also antimutagenic, antibacterial, and anticarcinogenic effects [21, 22]. Moreover, it has been shown that STS may be advantageous even after certain injuries. For example, in rats, a day of fasting can promote recovery following moderate but not severe damage in a controlled cortical impact injury model [23].

This manuscript proposes to review literature data for a better understanding of the correlation between the effects of the dietary restriction and response to anticancer treatment.

Dietary restriction-induced molecular changes

Until now, the restricted available data do not point to a single gene, pathway, or molecular mechanism underlying the benefits of the different dietary approaches. It is well known that the salutary effect is mediated in part by the negative regulation of nutrient-signaling pathways, including, in particular, the growth-promoting insulin-like growth factor 1 (IGF-1) receptor and its downstream effectors, such as extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K), which are known to regulate several detoxification enzymes [24] (Fig. 1).

The IGF-1 pathway influences both animal life-span and oxidative stress sensitivity. IGF-1 receptor-deficient mice showed a great resistance to oxidative stress [25]. The Forkhead box protein O1 (FOXO1), a downstream target of IGF-1/AKT signaling, is able to enter the nucleus, in the absence or reduction of IGF-1/AKT signaling, and to modulate genes involved in oxidative stress resistance, metabolism, and longevity [26–28].

Circulating IGF-1, in collaborations with other hormones and growth factors, plays an important function in the regulation of cell differentiation and proliferation and body size and also exerts a tumorigenic effect on a variety of tumors by promoting proliferation and inhibiting apoptosis [29, 30].

Consistent with the effect of calorie restriction and starvation (short- and long-term) in reducing growth factor signaling, fibroblasts isolated from mice deficient in the GH/IGF-1 pathway are resistant to oxidative stress, UV, heat, and genotoxins [31]. On the other hand, exposure of murine hepatocytes to IGF-1 reduces the levels of superoxide dismutases and catalase activity [32].

Moreover, it has been shown that a fasting period of 24 h does not alter the hepatic expression of many ABC family members but induces the expression of Abca1 (involved in cholesterol transport) and Abcg8 (involved in sterol transport) [33].

Dietary restrictions (DRs) also suppress the inflammatory response. Restricted rats have exhibited reduced mRNA expression levels of inflammatory cytokines and chemokines (IL-1β, TNF-α, and MCP-1) in various tissues such as the liver, kidney, and spleen [34]. Coherently, 4 weeks of DR decrease signs of illness (fever, cachexia, etc.), mitigating pro-inflammatory gene expression (for example, COX-2 and leptin) and increasing anti-inflammatory gene expression (e.g., SOCS3 and IL-10) [20].

Some researchers have submitted to serum starvation primary human myotubes, rat L6 myotubes, and human embryonic kidney cells for 24 h and assessed phosphorylation changes in the energy-sensing AMP-activated protein kinase (AMPK) and its downstream targets, including acetyl-CoA carboxylase (ACC), ERK1/2, and mammalian target of rapamycin (mTOR) pathway. Additionally, the phosphorylation of AMPK, ACC, and ERK1/2 reacted to serum starvation dynamically in a time-dependent way. Changes induced in the mTOR pathway after serum starvation can be associated with growth factor deprivation [3].

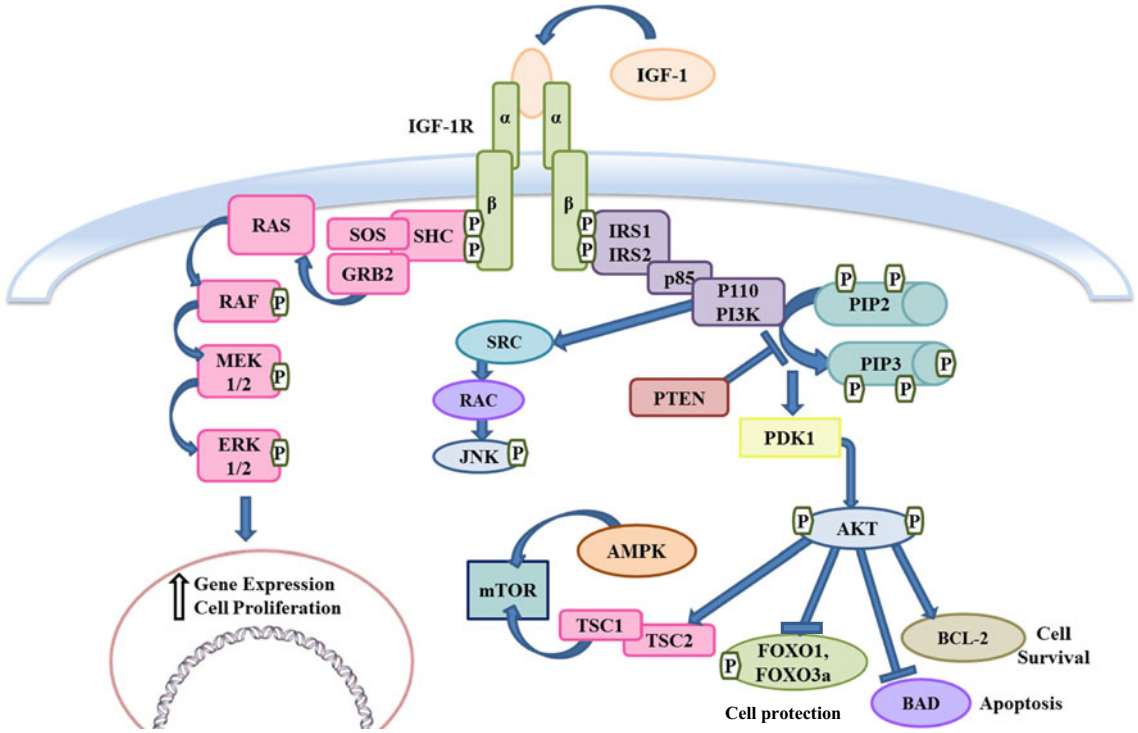

Fig. 1 Insulin-like growth factor-1 (IGF-1) signaling pathway. *IGF-1* insulin-like growth factor-1; *IGF-1R* insulin-like growth factor-1 receptor; *SHC* Src homology 2 domain-containing adaptor protein B; *SOS* Son of Sevenless; *GRB2* growth factor receptor-binding protein 2; *RAS* rat sarcoma viral oncogene homolog; *RAF* RAF-1 proto-oncogene, serine/threonine kinase; *MEK1/2* mitogen-activated protein kinases 1/2; *ERK1/2* extracellular signal-regulated protein kinases 1/2; *IRS1* insulin receptor substrate 1; *IRS2* insulin receptor substrate 2; *p85* phosphatidylinositol 3-kinase 85-kDa regulatory subunit alpha; *P110 PI3K* phosphatidylinositol 3-kinase, catalytic, 110-kDa, alpha; *PIP2* phosphatidylinositol 4,5-bisphosphate; *PIP3* phosphatidylinositol 3,4,5-trisphosphate; *PTEN* phosphatase and tensin homolog; *PDK1* pyruvate dehydrogenase kinase, isozyme 1; *AKT* V-Akt murine thymoma viral oncogene homolog 1; *BCL-2* B cell CLL/lymphoma 2; *BAD* BCL2-associated agonist of cell death; *FOXO1* Forkhead box O1; *FOXO3a* Forkhead box 3a; *TSC1* tuberous sclerosis 1; *TSC2* tuberous sclerosis 2; *mTOR* mammalian target of rapamycin (serine/threonine kinase); *AMPK* AMP-activated protein kinase; *SRC* SRC proto-oncogene, non-receptor tyrosine kinase; *RAC* Ras-related C3 botulinum toxin substrate; *JNK* c-Jun N-terminal kinase

Different dietary approaches may regulate genes involved in cellular proliferation, such as the insulin signaling adaptor (Irs2) and mitogenic hormone prolactin receptor (Prlr), in both normal and cancer cells [19]. It has been demonstrated that the PI3K pathway is important in determining the sensitivity of tumors to dietary restrictions. In particular, mutations that make PI3K constitutively active affect the response of cancer cells to dietary restrictions [35]. Instead, studies showed that STS had a greater effect in reducing glucose compared to calorie restriction diets, even when the CR caused an equivalent weight loss. This can be explained by the fact that STS and calorie restriction diets have distinct physiological responses. For example, short-term fasting induced a 70 % decrease in blood glucose that occurred within 60 h, while a 90 % CR diets caused only a 40 % glucose reduction after 96 h [21, 36].

Previous findings have clarified that serum starvation activates in cancer cells the ATM/Chk2/p53 pathway that sensitizes them to chemotherapy with cisplatin, probably due to a temporary loss of the coordination between cell proliferation driven by oncogenic mutations and the growth stimulated by growth factors [37].

Dong et al. [38] demonstrated, through in vitro studies using A549 non-small cell lung cancer cell lines, that serum starvation increases E-cadherin expression. E-cadherin is involved in the pathobiology of several types of cancer: the loss or dysfunction of E-cadherin is associated with increased lung cancer cell proliferation and invasiveness [39].

Braun et al. [40] observed that starvation induces the increase of p21 levels in MCF7 cell lines independently from p53 and this mitigates the efficacy of the Puma/Bax-dependent apoptotic signal (also induced by starvation). In addition, the anti-apoptotic function exerted by p21 in starved cells occurs upstream of mitochondrial permeabilization at the level of the Puma interactions with Bcl-x. Therefore, p21 protects cells against starvation-induced apoptosis. Furthermore, an important step for cellular apoptosis is the phosphorylation of H2AX (a variant of the histone H2A family) that is mediated by MAPK family proteins, such as JNK and p38. Several data showed that serum starvation induces strongly the phosphorylation of p38 and H2AX at Ser139 in a time-dependent

manner. These results indicate that H2AX phosphorylation is regulated by p38 during serum starvation. In addition, serum starvation increased the level of activated caspase-3, resulting in apoptosis stimulation [41].

Nutrient starvation puts cells in alarm and induces them to autophagy, a conserved self-eating process in which intracellular membrane engulf a part of cytoplasmic organelles for lysosomal degradation. Autophagy is a way by which cells under starvation condition transfer nutrients from unnecessary to essential processes [42]. The stimulation of autophagy by starvation needs the activation of poly(ADP-ribose) polymerase (PARP)-1, a nuclear enzyme switched on by DNA damage. During starvation, ROS that could induce the activation of PARP-1 are produced [43]. PARP-1 seems to be involved in the hydrolysis of ADP ribose: its lack, in fact, does not reduce ATP levels as much as when it is present [44]. As result, the permanence of AMPK in an inactive state and the consequent absence of the signal for mTOR inactivation were detected, leading to impaired autophagy. An interesting in vivo study suggested that PARP-1 regulates autophagy and makes available a link between the PARP-1 function and overall cellular response to nutrient starvation. Then, starvation, ROS production, and DNA damage cause PARP-1 activation that is required for starvation-induced autophagy [43]. It is well known that ROS-induced DNA damage consists of different lesions, including single-strand breaks (SSBs), double-strand breaks (DSBs), and oxidized DNA nucleotides, the most common of which is 8-oxo-7,8-dihydroguanine (8-oxoG). The latter type of damage requires the intervention of the base excision repair (BER) system, involving the repair enzyme 8-oxoguanine DNA glycosylase (OGG1). It has been observed that nutrient availability affects BER causing the loss of OGG1 both in vitro and in vivo. In particular, the induction of autophagy showed no consequence on OGG1 expression without starvation [45].

Dietary restriction and cancer

Tumor cells are exposed to numerous cellular stresses, such as oncogene-induced genotoxic [46], oxidative [47], and metabolic [48] stresses to which normal cells are not subjected. That is why tumor cells are more dependent on stress by supporting pathways for survival than normal cells.

Malignant cells undergo a series of genetic and epigenetic alterations that allow them to be both self-sufficient for growth and non-sensitive to anti-growth stimulation. Cancer cells express oncogenes that can continue to relay the effect of growth factor, while healthy cells are unable to grow in the absence of stimulation. This *independence* could be explained by the autocrine production of growth factors or by mutations that make constitutively active intracellular signal transduction proteins or membrane receptors. For example, factors overproduced by cancer cells are platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and IGF-1 [49]. Probably, the most important contribution regards alterations in genes coding for components of the Ras/Raf/MAPK and PTEN/PI3K/AKT pathways. In fact, mutated Ras alleles can render the cell proliferation independent from extracellular signals found in approximately a quarter of all cancers [50] and, in particular, in half of colon cancers [51].

In vitro serum starvation and in vivo short-term starvation reduce the levels of growth factors in normal cells [52, 53]. Furthermore, in the same cells, the depletion of paracrine communication signal of growth factors reduces the activity of proliferation signaling pathways and also the basal cellular metabolism. Consequently, cells enter in a proliferative/quiescent status [3]. Unlike healthy cells, it has been suggested that cancer cells cannot rapidly adapt to fasting and thus STS determines a differential stress resistance. Malignant cells, in fact, struggle to adapt to the loss of external growth factors by regulating autonomous growth stimulation and reprogramming their metabolism, thereby maintaining continuous proliferation [49]. This fundamental difference between healthy and unhealthy cells may explain why starvation condition protects normal cells without interfering with the killing of malignant cells [21, 54] (Fig. 2).

In vitro and in vivo studies demonstrated that fasting alone can modulate cell proliferation and apoptosis in different types of tumors by determining an increased cytotoxicity when combined with chemotherapy, the main treatment for tumor injuries. Several chemotherapy drugs harm DNA and cause cell death in part by promoting oxidative damage that involves not only tumor cells but also normal tissues (especially with high-dose chemotherapy) [55]. This increase in ROS may act synergically with fasting and chemotherapy [19]. It seems that the different types of dietary restriction selectively protect normal cells from chemotherapy toxicity, sensitizing simultaneously tumors to therapy, and STS is much more effective than calorie restriction or long-term fasting [21].

STS is able to sensitize various cancer types to chemotherapeutic agents. Some authors, in fact, showed that growth factors and glucose restriction slowed proliferation and increased cell death in 3 different murine cancer cell lines, while 24 h of fasting before and after drug treatment sensitized 15 of 17 cancer cell lines. They also evaluated the effect of fasting in a model of human metastatic cancer by applying five cycles of fasting for 48 h in immunosuppressed nude mice xenografted subcutaneously with human neuroblastoma cells and comparing the results with

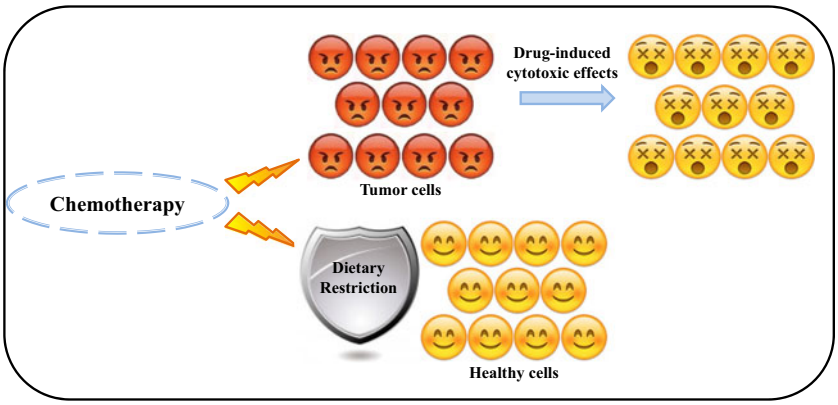

Fig. 2 Effects of dietary restrictions on effectiveness of chemotherapy in cancer cells

normally fed mice. After 34 days, fasting cycles and cyclophosphamide treatment reduced tumor size to less than a half of the one achieved in the treatment with cyclophosphamide or fasting alone [19].

STS followed by chemotherapy is not only safe and feasible but also helps to attenuate the side effects related to chemotherapeutic drugs. Some studies have shown that STS induces cardioprotective effects against the injury caused by doxorubicin [56]. Moreover, Raffaghello et al. [54] studied the effects of high-dose etoposide, a chemotherapeutic drug with a non-specific toxicity profile, in murine models undergone to fasting for 48–60 h, before the administration of a high-dose drug, and in a control group fed ad libitum. The latter group, after the treatment, showed many of the signs associated with the toxicity of etoposide, including the reduced mobility and the ruffled and posture alterations, while mice submitted to fasting showed no obvious signs of stress or pain. The beneficial effect of fasting was confirmed by comparing the mortality rate of mice in the two groups (43 % of the animals in the control group), and only one case in the fasting group died from acute toxicity by etoposide. A second group of mice was starved for 60 h and then treated with a dose of etoposide four or five times higher than the maximum dose recommended for humans. While non-starved mice died or showed toxicity, starved mice only lost the 40 % of their weight, which was regained after 1 week of re-feeding.

There is also an evidence of the benefits of the STS before chemotherapy in humans. Ten volunteers affected by different types of tumors were starved for 48–140 h before chemotherapy and 56 h after the treatment. All patients showed decreased chemotherapy-induced side effects [54]. A period of fasting after chemotherapy treatment could be relevant, because the combination of re-feeding and drug-induced DNA damage can increase the growth of aberrant foci in the liver, colon, and rectum. This can be explained by the hypothesis that prolonged fasting induces cell death and atrophy in the organs and thus cell proliferation stimulated by re-feeding can lead to a DNA damage, if high levels of toxins are present [57, 58].

Effects of dietary restrictions on the main tumors

During disease, the interactions between tumor and stroma cells are modified, producing a microenvironment that favors the primary tumor growth (remodeling, invasion, and angiogenesis) and its spreading (metastasis). Tumor microenvironment is heterogeneous and, in addition to the tumor cells, includes macrophages, fibroblasts, adipocytes, and endothelial cells that appear different from those of normal tissues [59]. Among these, adipocytes suffer the influence of dietary restrictions and physical exercise. This condition implies that dietary restrictions could be an effective method to favorably change the tumor microenvironment and its activities [60]. Adipocytes localized near the tumor mass are called "cancer-associated adipocytes" and show a reduction of adipose markers, such as HSL, APN, and resistin, and an increased expression of inflammatory cytokines (e.g., IL-6 and IL-1β) [61]. Adipocytes play an important role in cancer progression and may contribute to carcinogenesis and tumor invasiveness, since they are a source of pro-inflammatory cytokines, such as IL-6 and TNF-α, ROS, and matrix metalloproteases [62–65]. Moreover, adipocytes are able to secrete adipokines that increase angiogenesis, fibrosis, and inflammation by recruiting macrophages and endothelial cells inside the cancer microenvironment in a way mediated by NF-KB [66]. Dietary restriction can modulate the function of the tumor microenvironment by altering the size of adipocytes [63] and, consequently, reducing adipokine secretion, such as IL-6 [67]. Furthermore, dietary approaches are often associated with an increased life-span in mammalian and a better response to chemotherapy in various types of cancer. It is well known, in fact, that the bioavailability of several anticancer oral drugs changes because of food exposure. Chemotherapy

drugs are not the only cytotoxic strategy used for the treatment of cancer. Evidences suggest that caloric restriction might also be associated with radiation therapy (RT). Champ et al. [68] reported that CR can modulate pathways involved in resistance to treatment (such as IGF-1) and make cancer cells more sensible to cytotoxicity induced by radiotherapy.

The standard chemotherapy can enhance cellular metabolism by creating a tumor microenvironment rich in glucose and glutamine. Recently, as an alternative to standard treatment, metabolic therapies aimed to target metabolic alterations present in all tumor cells and which give a benefit to normal cells have been developed. For example, among the metabolic therapies that improved the prognosis of patients with glioblastoma multiforme and brain cancer, there is the calorie-restricted ketogenic diet (KD-R), which shows anti-angiogenic, anti-inflammatory, and anti-apoptotic effects [69].

Below we discuss some data in the literature concerning the effects of dietary restrictions on the main tumors.

Breast cancer

Breast cancer is the most common cancer and represents the first cause of the cancer death in women worldwide [70]. A case report has shown the effect of a fasting period on Caucasian women affected by breast cancer. The first case was that of a 51-year-old woman (stage IIA) who has received adjuvant chemotherapy (docetaxel and cyclophosphamide) and has been subjected to fasting 140 h before and 40 h after treatment. During fasting-chemotherapy cycle, the patient showed no side effects in contrast to when she has undergone chemotherapy alone. Even the complete blood count (CBC) appeared best if the treatment was preceded by a period of fasting. Another case was that of a 53-year-old woman (stage IIA, HER2+) who has been exposed to four chemotherapy cycles (with docetaxel and cyclophosphamide) and fasting for 64 h before and 24 h post chemotherapy. Negligible side effects were observed, including only mild weakness and short-term memory impairment. The third case was represented by a 48-year-old woman treated with four cycles of doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab. During treatment, the patient was subjected to fasting for 60 h prior and 5 h post drug administration, showing no side effects associated with these drugs. The last reported case was that of a 78-year-old woman (HER2+) submitted to mastectomy and to six cycles of chemotherapy with carboplatin, docetaxel, and trastuzumab. The patient adopted fasting periods of variable lengths during therapy and, despite this, has not been reported severe side effects [71]. Therefore, it becomes apparent that a short period of fasting in association with chemotherapy treatment improved patient's tolerability, reducing side effects even if underlying molecular mechanisms are unclear. Factors related to the DNA repair systems or apoptosis may be involved [72]. One of these is REV1, a DNA polymerase involved in DNA repair, whose role is to control cell metabolic fate. In a recent work, REV1 was indicated as a binding partner of p53 and, consequently, as a regulator of its activity. Under fasting conditions, SUMO2/3 (small ubiquitin-like modifier) induces changes in REV1 by increasing the apoptotic effects of p53 on breast cancer cells. The regulation of REV1 could be used as a non-toxic strategy to increase p53-mediated cell death and thus to improve the effectiveness of treatment [73].

Ovarian cancer

Ovarian cancer is the third most common gynecological cancer worldwide [74]. In vitro studies suggested that serum starvation reduces cell proliferation by inducing G1 arrest in human ovarian cancer cells (SK-OV-3), through the suppression of Skp2-dependent CDK2 activity and Skp2-independent CDK4 activity. Skp2 is an ubiquitin ligase that positively regulates cell cycle by inducing degradation of p27, resulting in CDK2-induced progression from G1 to S phase [75].

A clinical study reported the case of a 44-year-old Caucasian woman affected by ovarian cancer who, after a series of drug resistances, has been treated with antineoplastic drugs in combination with a fasting period of 62 h prior and 24 h after treatment. STS has been shown to improve the CBC [71].

Colorectal cancer

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide [74]. Among the initial modifications causing the CRC onset, there is the suppression of the serotonergic system that seems to be related to a high-fat diet [76]. Moreover, this type of diet enhances the formation of preneoplastic lesions and consequently promotes CRC tumorigenesis [77]. However, it has been shown that, during the advanced stages, the disease can induce a reduction of serum total cholesterol levels [78]. Kaska et al. [79] had evaluated the effects of a preoperative fasting period in CRC patients, observing no clinical benefit. Conversely, intake of nutrients seems to be a protective factor against surgical trauma. However, results about the beneficial effects of dietary restrictions are conflicting. Indeed, some authors reported that nutritional deficiencies promote tumorigenesis because the lack of certain nutrients increases chemically induced carcinogenesis in preclinical models [80]. Furthermore, another study evaluated the combined influence of a carcinogen (1,2-dimethylhydrazine or DMH) and food deprivation regimen in murine models. Food deprivation has been shown to induce an increase of the lipid peroxidation

processes in liver and colon tissues, suppressing the serotonergic system in the colon [81].

Lung cancer

Lung cancer represents the most common cause of cancer death worldwide [82]. The therapy of choice for patients with locally advanced or metastatic non-small cell lung cancer (with or without epidermal growth factor receptor (EGFR) mutation) involves the use of erlotinib (an EGFR tyrosine kinase inhibitor). Currently, its recommended dose is 150 mg daily, either 1 h before or 2 h after a meal. Katsuya and colleagues [83] observed that these two types of fasting determine a different drug absorption, resulting in increased therapeutic effectiveness when drug administration occurs 2 h after meal. Also, the authors found no major differences in terms of toxicity or bioavailability between the two conditions [83]. An interesting clinic case is represented by a 61-year-old Caucasian woman with poorly differentiated non-small cell lung cancer. During chemotherapy cycles, the patient experienced numerous side effects that have been attenuated after the implementation of fasting 48 h before and 24 h after chemotherapy [71].

Prostate cancer

Prostate cancer is the second most common cancer in men and the fifth leading cause of cancer death [74]. A high-fat diet and a sedentary lifestyle can be considered risk factors for the onset of prostate cancer by changing the amount of hormones and growth factors in the serum. An interesting study has recruited men with prostate cancer randomly divided into two groups: one group fed with a low-fat diet and the other without restrictions. After 4 weeks, the serum was collected from the patients and cultured with LNCaP prostate cancer cells. The serum of both groups was not different in terms of serum prostate-specific antigen (PSA), sex hormones, insulin, IGF-1 and IGF-2, and insulin-like growth factor-binding proteins, but serum triglyceride and linoleic acid (omega-6) levels were decreased in the low-fat diet group (in which omega-3 levels were increased). It was observed that LNCaP cells in contact with the serum of patients with low-fat diet grew very slowly. Thus, a reduction in serum fatty acid levels may induce a decrease in human LNCaP cell growth [84]. A case report described the effect of a fasting period on the response to an antineoplastic treatment in two Caucasian men affected by prostate cancer. The first case was that of a 74-year-old man with stage II prostate adenocarcinoma and submitted to prostatectomy. After therapy failure and severe side effects, the patient was submitted to 60 h of fasting prior and 24 h post chemotherapy. As result, a reduction of side effects and PSA levels was observed compared to previous cycles without STS. Similar results were obtained in a 66-year-old man with prostate adenocarcinoma subjected to fasting for 60–66 h prior and 8–24 h after chemotherapy [71].

The beneficial effect of STS may be also observed when the natural compound Guttiferone F (a prenylated benzophenone derivative) is used. Guttiferone has been shown to inhibit cell proliferation in prostate cancer cell lines (LNCaP and PC3) submitted to serum starvation. In this case, the compound leads to DNA fragmentation; causes the entry of cells in the G1 phase; stimulates mitochondria-dependent apoptosis, by regulating the Bcl-2 family proteins; attenuates the androgen receptor expression and ERK1/2 phosphorylation; but activates JNK and calcium ion flow. The authors hypothesized that the combination of dietary approaches and Guttiferone F could increase the antitumor effect without causing cytotoxicity in vivo [85].

In vivo studies investigated the effects of intermittent calorie restriction (ICR) on mice xenografted with prostate cancer cells or transgenic adenocarcinoma mouse prostate (TRAMP) models. Bonorden et al. [86] observed that ICR (with a CR of 50 % lower than the classic feed) delays the onset of cancer in TRAMP mice. If future studies will confirm this data, STS could become an interesting strategy for prostate cancer treatment.

Conclusions

Since dietary approaches represent an easy tool in delaying aging, healing from damages, and preventing the onset of age-related diseases, they may become efficient allies for cooperating in the treatment of tumors, even though STS seems to be more tolerated by sick patients. It is essential to understand each change or hidden feature induced by the processes described above to reap the benefits related to fasting.

The currently available data have associated the various dietary approaches to numerous biological processes (from cellular proliferation and vitality to inflammatory response) and to the response to the chemotherapy. Recent studies have reported that dietary restriction induces molecular changes in genes, including IGF-1 and its receptor, as well as downstream effectors. The modification regards also inflammatory cytokines and chemokines, such as IL-1β and TNF-α, and elements associated to apoptosis (Bax/Bcl-x). However, additional insights are needed. Moreover, it might be interesting to get more results in humans in order to ascertain the effect of fasting and create standard protocols that are able to correlate dietary approaches with chemotherapeutic treatments.

Compliance with ethical standards

Conflicts of interest None

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