Intermittent Fasting and Cancer

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ABSTRACT

Intermittent fasting (IF) has been shown to confer several physiological benefits, such as improved glucose regulation, stress resilience, suppression of inflammation, and in relation to cancer, tumor growth inhibition. These benefits can be accomplished through several mechanisms, such as induction of autophagy, mitophagy, autophagic cell death, and changes in the cellular metabolic environment. The nutritional restriction is a promising protocol to modulate autophagy and enhance the efficacy of anticancer therapies while protecting normal cells. IF may offer cancer patients an effective and less toxic adjuvant treatment for cancer. In addition, IF has shown benefits when combined with the use of chemotherapeutic drugs resulting in a decrease in side effects and an increase in the effectiveness of the drugs. This article discusses the evidence in support of dietary restriction, specifically IF, as a tool that may provide physiological and epigenetic benefits in the management of cancer.

Keywords: Intermittent fasting; Caloric restriction; Autophagy; Cancer; Fasting; Mitophagy; Short-term starvation

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INTRODUCTION

Intermittent fasting (IF) is a form of short-term caloric restriction. IF protocols and intervals vary, but common practice is to abstain periodically from eating food longer than the normal overnight fast.[1,2] Because the length of the fasting periods varies, it is important to consider what metabolic changes occur during the different stages of fasting.[3] Klein found that the breakdown of stored triglycerides and fat oxidation occurs during short-term fasts in which individuals abstain from food for 18 to 24 hours. Increased lipolysis has been observed, which may cause mobilization and utilization of fatty acids within adipocytes and oxidation in other tissues.[3,4] These processes may explain the benefits of IF for the treatment and prevention of obesity.[5] To gain maximum benefits, it is thought that feeding times should be scheduled to align with circadian rhythms and activities so that timely nutrient metabolism favors healthy physiology.[6,7]

IF has been shown to offer many health benefits in addition to weight loss, such as promotion of anti-inflammatory responses, cardioprotective effects, increased insulin sensitivity, reduction of oxidative stress, and promotion of autophagy.[8] Stressful stimuli, like hypoxia or caloric restriction, are specifically linked to the induction of autophagy.[9,10]

Autophagy, or macroautophagy, is a catabolic process in which a double membrane vesicle or autophagosome engulfs unused cellular proteins and damaged organelles for lysosomal degradation. Degraded substrates may then be recycled to fuel bioenergetic metabolism and cellular repair mechanisms. The process of macroautophagy can also lead to cell death or "autophagic cell death," as a result of the accumulation of autophagosomes and autolysosomes in the cytoplasm.[11–13] The effects of fasting and autophagy are still under study, but many researchers propose that IF could help with the treatment and eradication of tumors and cancer cells.[14–19]

INTERMITTENT FASTING AND CANCER

The metabolic effects of caloric restriction on cell metabolism may offer an advantage in the prevention and treatment of cancer. A fasting mimicking diet (FMD) is a high-fat, low-calorie IF method for 5 days every month.[20] Some researchers have proposed that fasting or FMDs promote broad variations in growth factors and in metabolite levels, creating environments that can reduce the capability of cancer cells to adapt and survive, thereby improving the outcomes of cancer therapies.[20] Data collected from 2413 women with breast cancer without diabetes demonstrated that overnight fasting for less than 13 hours can have a significant increase in breast cancer recurrence. For every 2-hour increase in fasting duration, there was a significant reduction in hemoglobin A1c.[6] In addition, IF is thought to protect normal cells (but not cancer cells) from the toxic effects of chemotherapy and promote cell regeneration in normal tissues. Fasting seems to improve the response to chemotherapy by several mechanisms including the following[21]:

- Enhances DNA repair in normal cells but not in malignant cells
- Improves autophagy mechanisms as a protection against damage to organelles
- Promotes apoptosis by both increasing tumor cell susceptibility to apoptotic stimuli, and averting apoptosis-mediated damage to normal cells
- Decreases regulatory T cells and enhances stimulation of CD8 cells

Quantitative redox proteomic studies have allowed estimations that predict that many proteins contain conditionally disordered regions that are likely redox-sensitive and thereby enable the transition from disorder to order or order to disorder conditional on oxidation or reduction.[22] In addition, protein misfolding may occur secondary to oxidative stress and other causes. Accumulation of misfolded proteins can lead to mitochondrial abnormalities, genetic instability, and cancer. Fasting may enhance the ability of mammalian cells to clear misfolded and aberrant protein, thereby facilitating immune surveillance. A study showed that intense exercise and fasting improve the ability of human and mouse cells to remove misfolded damaging proteins. This study revealed that the cells can activate a protein-processing mechanism, which allows them to adapt their protein content to shifting demands and new conditions.[23]

A pilot study was conducted with 14 subjects with metabolic syndrome who fasted for more than 14 hours daily for 4 consecutive weeks and were tested for proteomic analysis using nano ultra-high-performance liquid chromatography–tandem mass spectrometry. They found a significant fold increase in the levels of several tumor suppressors and DNA repair gene protein products (GPs) at the end of the fourth week. Also, a significant reduction was detected in the levels of tumor promoter GPs at the end of the fourth week. Fasting also induced an anti-diabetes proteome response by upregulating the crucial regulatory proteins of insulin signaling at the end of the fourth week. Participants demonstrated a significant reduction in body mass index and waist circumference, and improvement in blood pressure that manifested simultaneously with the anticancer, anti-diabetes serum proteome response. These findings suggest that IF for 14 hours actively modulates the respective genes and can be an adjunct treatment in metabolic syndrome.[24]

INTERMITTENT FASTING AND CHEMOTHERAPY

In a series of experiments where mice received subcutaneous injections of human neuroblastoma cells, tumor growth was found to be impeded by several cycles of fasting.[25–27] Mice that did not undergo IF had tumors double the size or more of fasted mice. More importantly, when using doxorubicin or a chemotherapy cocktail, fasting mice had significantly better survival than mice not fasting.[27] It was hypothesized that tumor cells compensated for the lower concentrations of extracellular glucose and growth factors by increasing DNA translation. This response had a tradeoff, however, and may have consumed even more energy, eventually promoting oxidative stress and cell death.[27]

Chemotherapeutic drugs such as cyclophosphamide (CP) increase DNA damage and cell death. Fasting has been shown to have a similar effect on cancer cells. In a study where mice received subcutaneous injections of breast cancer cells, two cycles of 48-hour fasting were found to be as effective as two cycles of CP.[27] Fasting cycles combined with CP maintained the size of the tumor to less than half the size observed in mice treated with CP only and fed ad lib. In a similar study, when fasting was combined with the chemotherapy drug doxorubicin (10 mg/kg), tumor progression was severely retarded.[27]

Cancer cells can modify their metabolism from oxidative phosphorylation to fermentation. This metabolic change, known as the Warburg effect, limits cell energy and results in an epigenetic expression that leads to malignancy.[28] For example, histone H2B monoubiquitination (H2Bub1) is an epigenetic pathway that negatively regulates the Warburg effect and tumorigenesis in human lung cancer cells. This pathway is regulated by pyruvate kinase M2 (PKM2), the rate-limiting enzyme of glycolysis. It has been proposed that this pathway controls the expression of various mitochondrial respiratory genes, which are essential for oxidative phosphorylation.[29] Fasting causes an anti-Warburg effect that promotes apoptosis in the colon cancer model. The cytotoxicity of oxaliplatin (OXP) combined with 48 hours of fasting was tested in the progression of CT26 colorectal tumors. Fasting potentiated the effect of OXP on the suppression of carcinoma growth. A reduction in the availability of glucose and amino acids reduced the expression of the glucose transporters Glut1 and Glut2 which reduces the glycolytic rate. The anti-Warburg effect is also associated with increased activities of complexes I, III, and IV of the respiratory chain, leading to the production of increased amounts of free oxygen radicals that are proposed to cause oxidative damage to the nuclear DNA. It was shown that fasting reduces the average tumor glucose consumption. This glucose reduction effect appears to potentiate the pharmacological effects of chemotherapy.[30–32]

Fasting may reduce the adverse effects of chemotherapy.[16,33–35] In a case series, 10 patients diagnosed with advanced stages of various cancers including breast, esophageal, prostate, and lung cancer, voluntarily fasted between 48 and 140 hours before chemotherapy and for 5 to 56 hours following chemotherapy. Subjects received an average of four cycles of various chemotherapy drugs in combination. Six patients received either chemotherapy alone or chemo-fasting treatments. Fasting reduced side effects such as fatigue, weakness, and gastrointestinal complications. Symptoms such as fatigue and

weakness were significantly reduced ($P<0.001$ and $P<0.00193$, respectively), while vomiting and diarrhea were essentially absent in the fasting group. In addition, fasting did not interfere with the chemotherapeutic effect of tumor reduction. This study supports the concept that fasting is safe during chemotherapy, that it reduces some adverse effects, and that it does not interfere with the therapeutic effect intended.[18]

INTERMITTENT FASTING, CHEMOTHERAPY, AND STRESS RESISTANCE

The protective effect of fasting against chemotherapy-induced toxic side effects may involve a reduction in anabolic and mitogenic hormones and growth factors such as insulin and insulin-like growth factor 1 (IGF-1) as well as upregulation of several stress resistance proteins.[36,37]

Differential stress resistance (DSR) is the term used to describe how, for example, fasting induces protection of normal cells, but not oncogene-driven cells, by blocking the activation of oncoproteins such as Ras, Tor, and PKA. In an animal model, Raffaghello and colleagues showed that short-term starvation (48 hours) protected normal cells against high-dose chemotherapy, but not neuroblastoma cells.[25] Given that activation of the IGF signaling pathway is a crucial prerequisite for malignant transformation, it has been proposed that the reduction in circulating IGF-1 and extracellular glucose levels caused by starvation-dependent DSR is in part responsible for protecting normal cells, but not cancer cells, against chemotherapeutic agents. Subgroup analysis of a randomized controlled trial revealed that only energy restriction regimens of 50% or greater of normal daily energy intake were able to significantly reduce IGF-1 levels. The percentage restriction of daily energy intake was found to have an inverse correlation with plasma IGF-1 levels ($P=0.04$).[38] Fasting can cause a rapid switch of cells to a protected mode in association with decreased levels of glucose, IGF-1, and other proteins and molecules that result in the protection of mammalian cells from several toxins, including chemotherapy. When oncogenes are expressed, it prevents the cellular switch to this stress resistance mode. Fasting for 48 hours or longer protects normal mammalian cells but not cancer cells from chemotherapy, an effect named "differential stress resistance."[25,26,39] Although reduced IGF-2 is important in the protection of chemotherapy and DSR, the exact mechanisms have not been elucidated. It has been suggested that negative regulation of the nutrient signaling pathway is involved. Reduction in serum IGF-1 levels, and growth factors, will affect downstream growth regulators such as mammalian target of rapamycin (mTOR), Akt, and Ras.[40]

INTERMITTENT FASTING, AUTOPHAGY, AND CANCER

Defective autophagy predisposes healthy cells to undergo malignant transformation. Many researchers hypothesize that the induction of autophagy by short-term starvation induces metabolic and biochemical pathways that may improve cancer treatment outcomes. However, the level of activation or inactivation of autophagy is important as extensive autophagic action promotes cell death.[13] The autophagic process is regulated by a series of proteins, such as mTOR, associated with cell proliferation, stress, and cancer progression.[41] Since autophagy inhibits cancer cell survival and induces cell death, it suppresses tumorigenesis. However, it may also favor tumorigenesis by promoting cancer cell proliferation and tumor growth.[42,43]

An important process often observed during autophagy is known as mitophagy or mitochondrial autophagy. During mitophagy, dysfunctional mitochondria are tagged and engulfed. Failure of mitophagy has been linked to tumor promotion.[10] The complex processes that lead to failed mitophagy result in reactivation of the Warburg effect and promotion of aerobic glycolysis, which favors tumor growth.[44] Multiple oncosuppressor genes, such as *PTEN* and tumor protein TP53, support autophagic responses. In contrast, several proto-oncogenes, such as *BCL2, AKT1*, and the epidermal growth factor receptor (EGFR), inhibit autophagic responses. For example, the anti-apoptotic protein Bcl-2 has an anti-autophagic effect by inhibiting Beclin 1.[45] Tumor-promoting activity has also been noted during the autophagic response.[46]

Autophagy is also critical for optimal immune function. It has been proposed to be a way to increase the effectiveness of immune therapy, chemotherapy, and/or radiation therapy.[47]

Given the complexity of autophagy, to have the best responses in cancer treatment, it is necessary to consider the type of cancer and its metabolic pathways. Short-term fasting, caloric restriction mimetics, or treatment with several chemically unrelated autophagy-inducing caloric restriction mimetics can improve the inhibition of tumor growth by chemotherapy *in vivo*.

The role of autophagy is dynamic, playing a tumor-suppressive or tumor-promoting role in different environments and phases of cancer development. Early in tumorigenesis, autophagy provides a survival pathway and quality-control mechanism, preventing tumor initiation and suppressing cancer progression.[48]

The autophagy effect improving tumor growth inhibition was dependent on the presence of T lymphocytes.[49] Given these findings, individualized treatment and diet may increase the effectiveness of cancer treatments and may further help with tumor growth inhibition and tumor burden reduction.

CONCLUSION

Fasting can lead to a decrease in growth factors and metabolites, creating an environment in which it is difficult for cancer cells to adapt and survive. In addition, fasting is thought to be protective against the effects of chemotherapy in normal cells and promote regeneration in normal tissues.[50] Autophagy is, however, a dichotomous process. Depending on the type of tumor, the tumor stage, and the tissue affected, autophagy will be different. Autophagy may inhibit tumorigenesis, but the loss or mutation of normal autophagic genes leads to increased tumorigenesis.[51] Many other variables may be involved in this complex process; for example, it is possible that the particular distribution of macromolecules (simple sugars vs. proteins or lipids) ingested following the fasting period may divert the physiological state to either promoting or inhibiting tumorigenesis. Thus, further research on the topic must be carried out to provide a deeper and more specific understanding of dietary restriction and cancer. The metabolic mechanism of IF could provide an important tool for the treatment and, potentially, the prevention of malignancy.

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