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# The Effect of Fasting on the Important Molecular Mechanisms Related to Cancer Treatment

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**ABSTRACT**

Fasting does have remarkable benefits in the treatment of cancer and another diseases such as metabolic syndrome, diabetes, and a multitude of other chronic diseases. It has been determined that fasting could play an important role during cancer treatment and progression via the regulation of insulin-like growth factor-1 (IGF-1) as well as other growth factors. Also, it has been shown that fasting would enhance the chemotherapy effect in cancer patients, selectively protects normal cells and organisms from chemotherapy toxicity, while simultaneously sensitizing tumors. In this article, we discuss the benefits of fasting in the treatment of cancer through several different molecular pathways.

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## Introduction

Cancer, also known as a malignant tumor, is a cluster of diseases involving abnormal cell growth with the potential to spread or invade to other parts of the body (1). Not all tumors are cancerous, but the cancerous could metastasis, which is the spread of cancer to other locations in the body. The new tumors are called metastatic tumors, while the original is named the primary tumor. Almost all cancers can metastasize and spread (2). Metastasis is very common in the late stages of cancer, and it can occur through the lymphatic system or the blood or both. The typical steps in metastasis are local invasion, intravasation into the lymph or blood circulation through the body, extravasation into other tissues, proliferation, and angiogenesis. Angiogenesis is a physiological process through which new blood vessels form from pre-existing vessels. It is different from vasculogenesis, which is the *de novo* formation of endothelial cells from mesoderm cell precursors (3). Cancer genetics is now one of the fastest expanding medical specialties worldwide. At the molecular level, cancer occurs via by mutation(s) in DNA, which result in aberrant cell proliferation. Most of these mutations are acquired and occur in somatic cells. However, some people inherit mutation(s) in their germlines (4). The mutation(s) arise in two classes of cellular genes: oncogenes and tumor suppressor genes. Cancer can be treated by surgery, radiation therapy, chemotherapy, hormonal therapy, and targeted therapy (including immunotherapy such as monoclonal antibody therapies). According to recent studies, fasting does have remarkable benefits in the treatment, not only of cancer, but also in metabolic syndromes, diabetes, and a multitude of other chronic diseases which plague our modern society. Fasting can theoretically inhibit several critical pathways in the development and progression of cancer, while simultaneously causing malignancies more sensitive to treatments for instance chemotherapy and radiotherapy (5).

### *The effect of fasting on chemotherapy*

There are several recent studies demonstrating that fasting can enhance the

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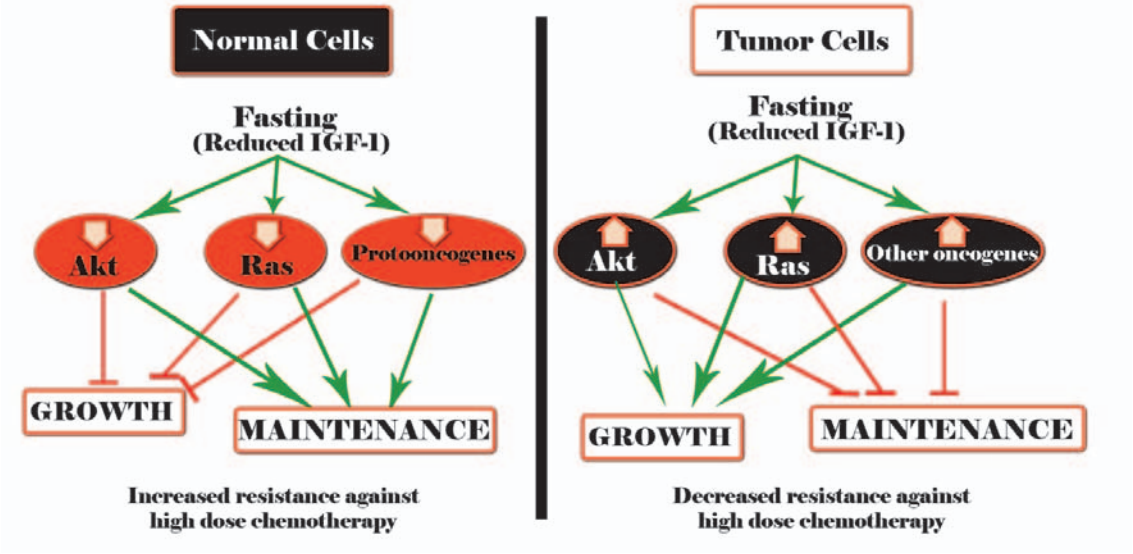


**Figure 1.** Fasting provides differential stress resistance (DSR) to chemotherapy

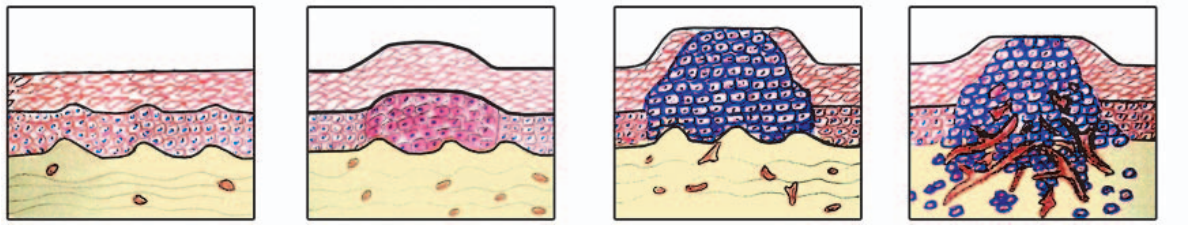

**Figure 2.** The switch to the angiogenic phenotype occurs during multistage tumor genesis. As malignancy develops, cell progress from a perivascular stage (normal to early hyperplasia) to a vascular stage (late hyperplasia to dysplasia to invasive carcinoma). Angiogenesis becomes clearly evident during dysplasia and is critical for further growth. Targeting tumor angiogenesis may be a novel strategy for preventing cancer

chemotherapy effect in cancer patients (6, 7). While, it is shown that chemotherapy is the most widely used strategy for the treatment of human cancers but the toxicity of the treatment makes it only partially effective particularly with advanced malignancies. Meanwhile, it has been recently demonstrated that fasting selectively protects normal cells and organisms from chemotherapy toxicity, while simultaneously sensitizing tumors (7, 8). This is occurring via the reduction of insulin and IGF-1 and consequently IGF-R1 inactivation (9, 10). For instance, one study has described that in 10 cases of cancer patients affected by different types of tumors, ranging from stage II breast cancer, stage IV esophageal, prostate, and lung malignancies showed that fasting with chemotherapy is safe and could lower common side effects associated to chemotherapy (11). It also causes a 70% decrease in circulating IGF-I levels, which restoring its levels during fasting reverses the protection against doxorubicin in mice (18). The effect of reduced IGF-I on protection against chemotherapy toxicity was also studied by using transgenic mice with a conditional liver-specific IGF-1 gene deletion (LID), which results in a 70–80% reduction in circulating IGF-I levels, similarity to that caused by fasting. LID mice showed better protection to commonly used chemotherapy drugs such as cyclophosphamide, doxorubicin and 5-FU, although they were not protected against the topoi-somerase inhibitor etoposide. Reducing IGF-I signaling could not only protect the organism but also reduce tumor progression (12). Altogether, this suggests that fasting has the potential to be translated into a mode of clinical intervention to protect patients against chemotherapy-induced toxicity (Figure 1).

### *Effect of fasting on angiogenesis*

Fasting inhibits angiogenesis (13). Tumors can only grow to the size of a pinhead (about 0.5 mm) without having a new blood supply. If the

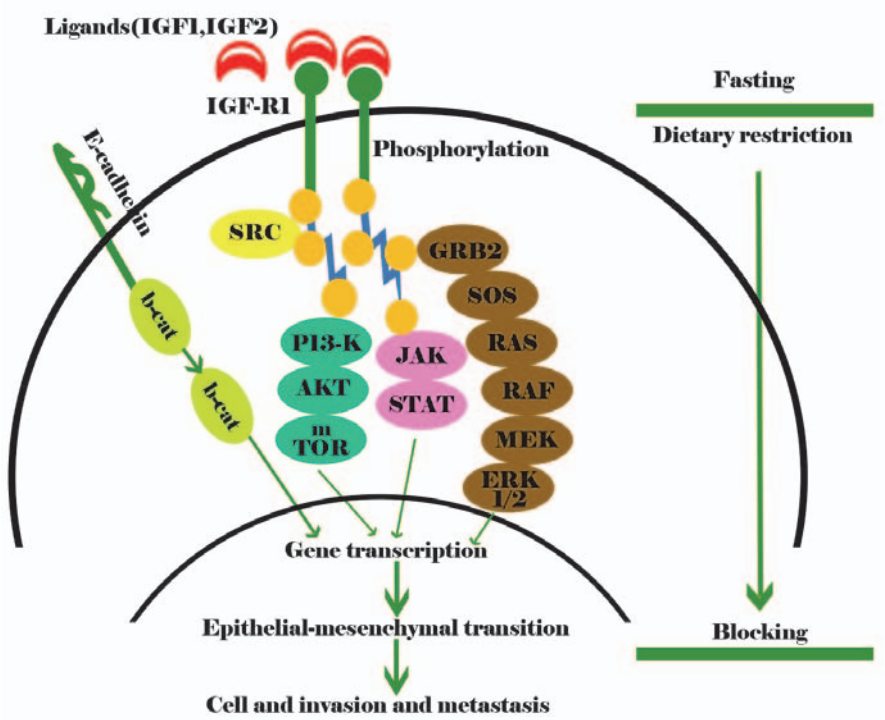


**Figure 3.** Schematic overview showing the effect of fasting and dietary restriction (DR) on IGF-R1 signaling pathways in cancer cells (18)

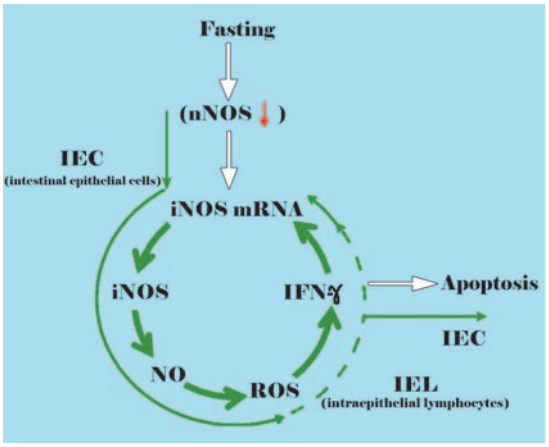


**Figure 4.** Schematic summary diagram of fasting-induced intestinal apoptosis. This schematic summary diagram depicts a possible role of nNOS in the regulation of iNOS activity upstream in the process of fasting-induced apoptosis. iNOS-derived NO may play a central role downstream in this process, inducing IFN-γ, and leading to intestinal epithelial cell (IEC) apoptosis. Note a close interaction between iNOS-released NO in IEC and intraepithelial lymphocyte (IEL)-derived IFN-γ through a ROS-mediated mechanism in the intestinal mucosa (19)

tumor cannot attract blood vessels, it prevents growing and never causes a problem. Through this mechanism, fasting could slow tumor growth (14).

In a study by Facchetti F et al. the angiogenic capacity of aorta decreased with ageing in the old rats. They have shown that caloric restriction work against the age-related changes caloric restrictions. Interestingly, mRNA endothelin-1 (ET-1) levels as well as ET-1 expression in aorta sprouting decreased both in their middle and in aged animals. It has been reported that mild and severe caloric restriction regimens could prevent ET-1 changes (15).

In another study it was observed that fasting reduces levels of ET-1 (16).

ET-1 has a direct angiogenic effect on peri-vascular and endothelial cells. It also has an indirect effect on the increased release of the potent pro-angiogenic substance vascular endothelial growth factor (VEGF), via hypoxia inducible factor-1. ET-1 also indirectly stimulates angiogenesis by stimulating cancer and fibroblasts cells to produce pro-angiogenic proteases. ET-1 is a new stimulator of tumor angiogenesis and it is necessary to carry out further examination as an anti-angiogenic treatment target (17).

### *Effect of fasting on metastasis*

Fasting and DR (dietary restriction) decreases IGF-1 secretion which as a result can

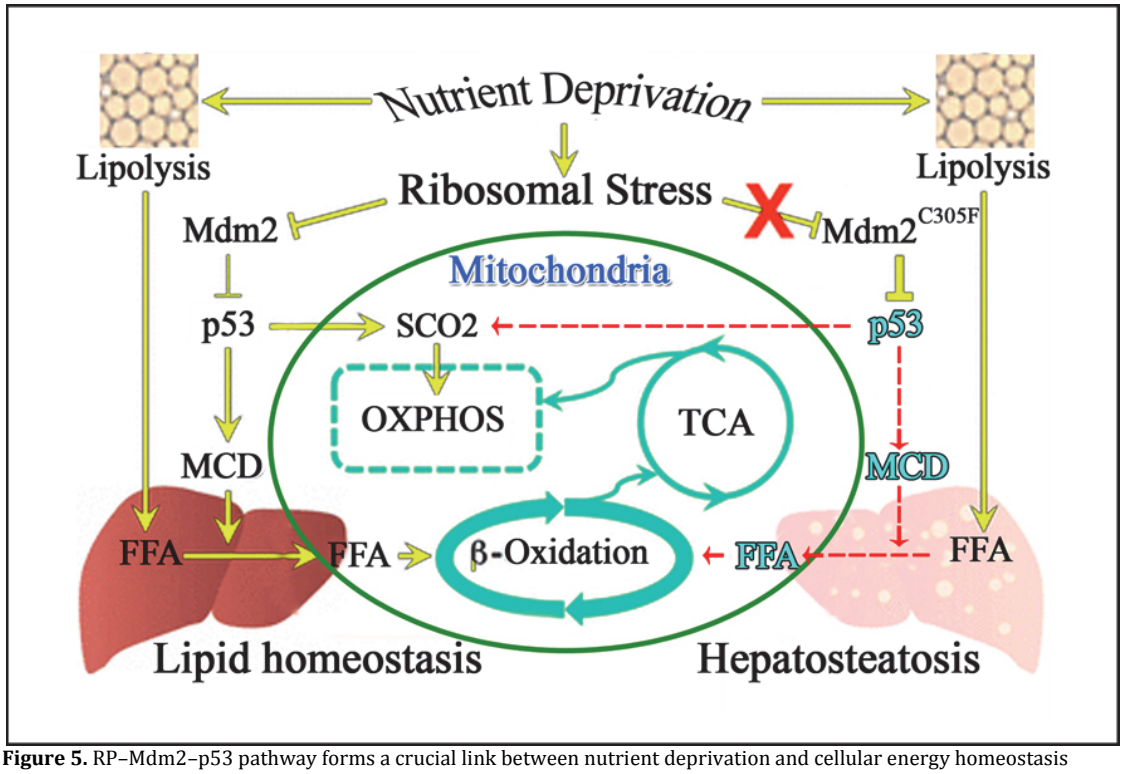


**Figure 5.** RP–Mdm2–p53 pathway forms a crucial link between nutrient deprivation and cellular energy homeostasis

reduce IGF-R1 downstream-signaling pathways, including Src/β-catenin, PI3K/Akt/Mtor, and GRB2/ERK pathway. They could be turned-off which cause blocking of the EMT (epithelial to mesenchymal transition) process with or without chemotherapy. Fasting and DR could also affect cell-cell adhesion molecules, consequently to decrease cell invasion and metastasis abilities in cancer patients (Figure 3).

### *Effect of fasting on apoptosis*

Fasting causes significant jejunal mucosal atrophy due to attenuated cell proliferation and enhanced apoptosis with increasing iNOS expression in intestinal epithelial cells (IEC), and thus, elevating jejunal nitrite levels. Nitric oxide (NO) is associated with intestinal apoptosis. However, aminoguanidine (AG) treatment histologically decrease apoptosis with inhibition of fasting-induced iNOS transcription, protein expression, and nitrite production in rat models of fasting. Junta Ito et al. also observed that fasting-induced ROS production and subsequent IFN-γ transcription, inhibited by AG treatment. Furthermore, they observed reduced transcriptional levels of nNOS, known to suppress iNOS activation physiologically. Their study suggests that fasting-induced iNOS activation in IEC could induce apoptosis mediators such as IFN-γ via a ROS-mediated mechanism, a possible role of nNOS in the regulation of iNOS activity in fasting-induced apoptosis (Figure 4) (19).

### *Effect of fasting on RP–Mdm2–p53 pathway and cellular energy homeostasis*

Nutrient deprivation induces lipolysis in adipocytes producing free fatty acids (FFAs). They could enter the liver to serve as a direct energy source or as a precursor for ketone body formation. In normal mouse liver, nutrient depletion causes ribosomal stress by inhibiting rRNA biosynthesis, which in turn inhibits Mdm2 (indicated by the smaller letters) and activates p53 to induce MCD expression. MCD facilitates the transport of FFAs into the mitochondrial matrix through CPT1α in order to be oxidized to acetyl-CoA by β-oxidation. Later, acetyl-CoA is oxidized through the TCA cycle to produce energy and “reducing equivalents” (NADH and FADH2), which are used for ATP synthesis by OXPHOS. P53 also induces the expression of SCO2, a crucial component of the electron transport chain, to promote OXPHOS. To sum

up, the action of the RP–Mdm2–p53 pathway maintains liver lipid homeostasis during the fasting state (Figure 5) (20).

## Discussion

Although fasting could play an important role in cancer treatment and progression, more studies and human trials are required before it can be determined whether fasting is a safe and effective way to reduce the toxic side effects of chemotherapy. There are a few reports, studying the side effects of fasting in animal models as well as cancer patients. The finding that rats deprived of protein increases Adriamycin-induced cardiomyopathy is troubling and suggests that cancer patients are not recommend for fasting. Some drugs such as Metformin, a drug used to treat type 2 diabetes, appears to mimics some aspects of caloric restriction in the body. This drug has been shown to reduce breast cancer risk and its recurrence. Metformin has been shown to enhance the effectiveness of Adriamycin chemotherapy.

Fasting for 48-hours was found to be sufficient to markedly suppress tumor progression in a mice model of breast cancer. It alone (without chemotherapy) caused more than a 50% decrease in tumor growth. When fasting was combined with chemotherapy, fasting was found to sensitize cancer cells to chemotherapy and further reduce tumor growth up to 90% compared to untreated mice. The protection against drug toxicity was due to reduced DNA damage to normal cells (21). However, we think that more molecular and cellular biological studies in addition to developing new animal models are necessary to determine the exact role of fasting in human cancers.

In conclusion, the effect of fasting in addition to increase apoptosis, and decrease cell invasion and metastasis and activation of p53 is to enhance the effectiveness of cancer chemotherapy, although more investigation is required.

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