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Intermittent Fasting (IF) Reduces Tumor Metastasis via Ras/MAPK, PI3K/AKT/mTOR, Wnt/β-Catenin, and HGF/c-Met Pathways

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Abstract

Several recent scientific interventions have been conducted to investigate the effects of intermittent fasting (IF) on tumor metastasis. It is well known that IF has a positive effect on reducing OS in the human body. OS is an important factor that leads to DNA damage and stimulates carcinogenesis through dysregulation of signaling pathways that are important for tumor survival and metastasis. Studies have demonstrated that mitogen-activated protein kinase (Ras/MAPK), phosphatidylinositol-3-kinase/mammalian target of rapamycin (PI3K/AKT/mTOR), Wnt Beta Catenin (Wnt/β-catenin), and hepatocyte growth factor/mesenchymal-epithelial transition factor (HGF/c-Met) are activated in response to the overproduction of OS and may result in carcinogenesis and tumor metastasis. In this review, we discuss the regulatory mechanism of IF in tumor metastasis by downregulating key OS pathways such as Ras/Raf/MAPK, PI3K/AKT/mTOR, Wnt/β-catenin, and HGF/c-Met.

Keywords

Intermittent Fasting, Tumor, Ras/MAPK, PI3K/AKT/mTOR, Wnt/β-Catenin, HGF/c-Met

1. Introduction

IF is another emerging avenue of research with superior outcomes in chronic disease control and comprises an eating pattern that alternates between periods of fasting and periods of normal eating on a regular schedule [1]. IF is a safe fasting method for achieving daily net reduction in caloric intake. IF can provide normal physiological function to the body, improve the immune system, and lead some tissues and organs to be more resistant to a variety of harmful stimuli that involve

oxidative, metabolic, ionic, traumatic, and proteotoxic stresses [2]. Di Francesco at el, found that IF can alleviate the development of many chronic diseases, including different forms of cancers, obesity, diabetes, vascular diseases, and neurodegenerative diseases [3].

From a pathophysiological perspective, IF can be explained in two ways. First, IF regulates proteins that regulate cellular functions, such as tumor suppression, mitochondrial biogenesis, and anti-inflammatory effects. Second, intermittent fasting activates kinases that modulate gene expression and metabolism, and AMPK-kinase regulates energy and stress resistance, as shown in **Figure 1**. [4]. In addition, IF causes a reduction in OS by mitochondrial and PI3K/AKT/mTOR pathways, thus lowering inflammation. Restriction of OS reduces the inflammatory response and decreases circulating some hormones and proinflammatory mediators, such as IGF-1, TNF-α, IL-6, matrix metalloproteinase-8 (MMP-8), matrix metalloproteinase-9 (MMP-9), and IL-1-beta in gingival crevicular fluid (GCF), which directly inhibits Ras/Raf/MAPK, PI3K/AKT/mTOR, Wnt/β-catenin, and HGF/c-Met in carcinogenesis [4] [5].

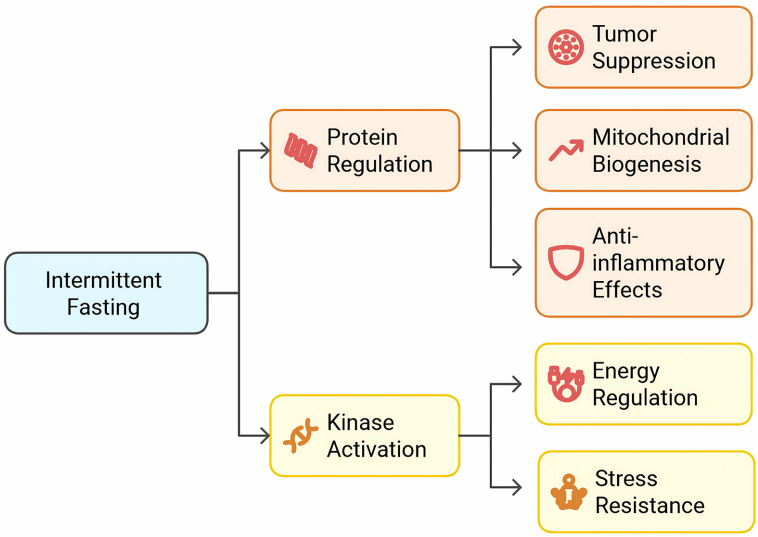

Figure 1. Schematic summary of the pathophysiology of intermittent fasting.

Chronic metabolic illnesses, such as cancer, have significant societal and economic repercussions, making it vital to find ways to avoid and regulate them [6]. Remarkably, IF is underpinned by current scientific evidence to be the most effective non-pharmacological potential therapeutic alternative for preventing and treating chronic inflammation caused by chronic diseases such as cancer [7].

2. IF and OS

IF has gained attention because of its potential impact on OS, a key factor in the development of chronic diseases, such as cancer, cardiovascular diseases, neurodegenerative disorders, and aging [8]. An imbalance between the production of ROS and the body's ability to counteract the harmful effects of antioxidants gives

rise to OS [9]. Published reports have shown that IF can reduce OS through several mechanisms, including changes in cellular metabolism (reducing glucose metabolism), enhancement of antioxidant defenses, improved mitochondrial function, and activation of autophagy [10].

IF alters glucose metabolism by inhibiting glycolysis, which in turn decreases ROS production and directly lowers oxidative stress levels in cells. Glycolysis inhibition is controlled during glucose metabolism, ketogenesis, and inhibition of insulin and insulin-like growth factor 1 (IGF-1) [11] [12]. Under normal physiological conditions, the body primarily relies on glucose metabolism to generate energy through a process called glycolysis. For this process, oxidative phosphorylation, which is a major source of ROS, must be initiated in the mitochondria [13] [14]. Overactivation of glucose intake increases the metabolic activity of the mitochondria, which leads to the overproduction of ROS as byproducts of electron transport. Upregulation of ROS production leads to overexpression of OS, which damages DNA and contributes to the development of various chronic diseases [15]. During IF, the body switches from using glucose as the primary fuel source to using fatty acids and ketones. This switching reduces reliance on glycolysis, which in turn lowers the production of ROS from glucose metabolism [13] [15].

Once the downregulation of glucose levels occurs due to IF, the body begins to break down stored fats into free fatty acids and convert them into ketones through a process called ketogenesis [16]. β-Hydroxybutyrate is one of the most common ketones used as an alternative energy source, and its metabolism generates fewer ROS than glucose. It is also known to activate protective pathways that further reduce the OS [17]. Fat oxidation reduces the demand for glycolysis and mitochondrial oxidative phosphorylation, both of which are major contributors to OS generation through ROS activation in a glucose-fed state [18].

IF also has a positive impact on the reduction of insulin and insulin-like growth factor 1 (IGF-1) production, both of which are anabolic hormones that promote glucose uptake and utilization in cells [11]. The overproduction of insulin and IGF-1 enhances glycolysis and oxidative phosphorylation, which leads to the expression of OS through ROS production [19]. Downregulation of insulin and IGF-1 expression by IF reduces the demand for glucose metabolism, which in turn decreases OS production. The inhibitory effects of insulin and IGF-1 signaling were shown to contribute to a slower cell proliferation rate [11] [20].

Brandhorst *et al.* explained how IF reduces OS by enhancing mitochondrial efficiency. He also reported that during fasting, the body undergoes metabolic reprogramming, shifting from glucose metabolism to fatty acid oxidation, which reduces the overall production of ROS, which are byproducts of cellular respiration [21]. The whole mechanism begins when IF stimulates mitochondrial biogenesis, which is the process by which cells increase their mitochondrial mass and improve their function [22]. The regulation of this process is controlled by the activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a key regulator of energy metabolism, leading to a reduction in

ROS production, thus lowering OS [23] [24].

IF also triggers activation of the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway, which is a major regulator of the antioxidant response. Nrf2 activation upregulates several antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase [25]. These enzymes play a crucial role in detoxifying ROS and protecting cells from OS damage by maintaining the cellular redox balance and preventing the accumulation of OS in proteins, lipids, and DNA [25] [26].

Fernanda *et al.* explain the importance of IF in the initiation of the autophagy, a cellular process that involves the degradation and recycling of damaged cellular components [27]. The mechanism of action occurs when a special process known as mitophagy selectively degrades dysfunctional mitochondria, prevents excessive ROS production, and promotes cellular health [28], this is explained in **Figure 2**. During IF, the majority of damaged mitochondria are eliminated, which leads to a reduction in overall ROS and OS. Autophagy plays a crucial role in maintaining mitochondrial health by allowing the turnover of old mitochondria, thus ensuring more efficient energy production with lower OS production [28] [29]. Furthermore, IF has been reported to reduce inflammation by inhibiting Nk-kβ, leading to a reduction in OS production by inhibiting the production of proinflammatory cytokines (such as TNF-α and IL-6) [30].

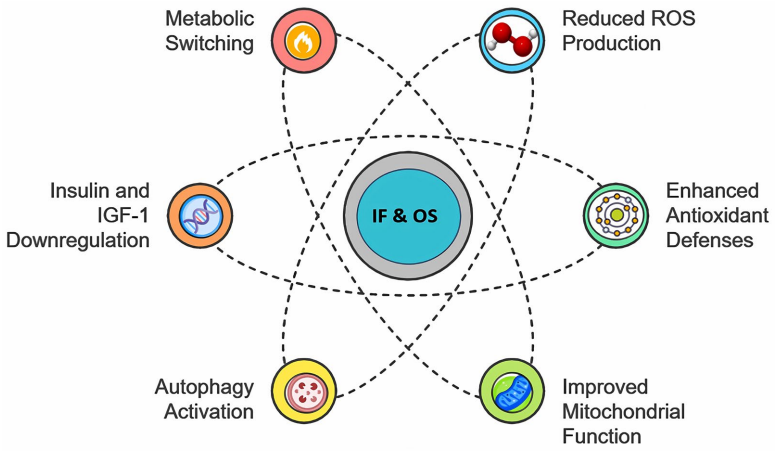

Figure 2. Schematic summary of the role of Intermittent fasting and oxidative stress reduction.

3. IF and Metastasis

Metastasis is a complex, multistep process that involves tumor cell proliferation, invasion, migration, and extravasation into distant organs [31]. Accumulating evidence suggests that OS and insulin-like growth factor 1 (IGF-1) are involved in modulating signaling pathways, gene expression, and cellular behavior, which later contribute to the metastatic capacity of cancer cells [32].

Notably, during IF, the level of IGF-1 declines, and the biological activity of IGF-1 is further compromised owing to increased levels of insulin-like growth

factor binding protein 1 (IGFBP1) [33]. This reduction occurs because fasting decreases the production of insulin and growth hormone (GH), which are key regulators of IGF-1 synthesis [34]. IGF-1 is a hormone that is structurally similar to insulin and plays a significant role in cellular growth, differentiation, and survival [35]. The upregulation of IGF-1 leads to increased production, especially in chronic conditions such as cancer. The overproduction of IGF-1 stimulates cell proliferation, prevents apoptosis (cell death), and enhances cellular survival mechanisms, creating an environment conducive to tumor growth [35] [36]. In chronic disease, IF was shown to affect the signaling cascades by inhibiting the downstream signaling by reducing glucose and/or IGF-1 levels, which are the key mediators of the cellular effects of fasting [1]. The inhibited signaling cascades are Ras/MAPK, PI3K/AKT/mTOR, Wnt/β-Catenin, and HGF/c-Met, which regulate the expression of proteins involved in adaptive cellular processes, including the inhibition of cell proliferation, induction of apoptosis, autophagy, DNA repair, genomic stability, carcinogen-detoxification, and inhibition of metastasis [1] [37] [38] as shown in **Figure 3**. It has also been reported that elevated levels of IGF-1 contribute to oxidative stress by activating mitochondrial activity and other metabolic processes that produce OS through ROS. OS production fuels tumor cell proliferation, growth, survival, and metastasis, which occur under stressful conditions. Simultaneously, OS can further activate IGF-1 signaling, creating a feedback loop that promotes cancer progression [37] [39].

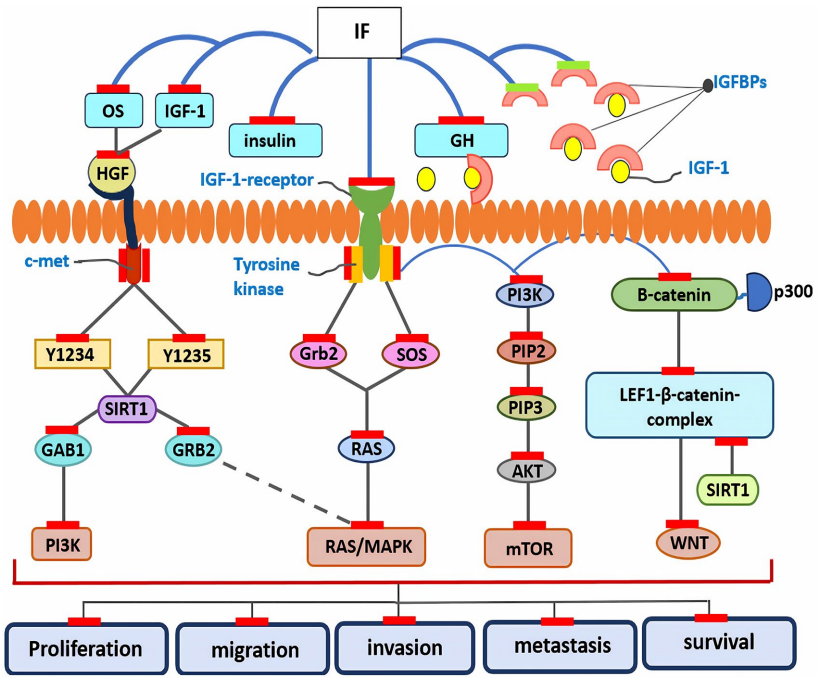

Figure 3. Schematic summary of the role of IF on Ras/MAPK, PI3K/AKT/mTOR, Wnt/β-Catenin, and HGF/c-Met pathways. Red line-represent inhibition and green line represent activation.

In normal physiology, the body enters a state of reduced anabolic activity

during IF. The liver, which is primarily responsible for producing IGF-1 in response to growth hormone (GH), decreases the IGF-1 output [40]. This phenomenon can be explained by five aspects: reduction in IGF-1 production, lower circulating levels of IGF-1, decreased IGF-1 expression, enhanced IGF-1 binding proteins (IGFBPs), and metabolic switch to ketosis [41].

The reduction in insulin secretion during IF is a key regulator of growth hormone activity. Downregulation of insulin production leads to reduced stimulation of GH receptors in the liver, which in turn leads to decreased IGF-1 production. However, during IF, there is less sensitivity to GH, which further reduces the production of IGF-1 [7]. A decrease in IGF-1 sensitivity or production results in a low concentration of IGF-1 available to bind to its receptors (IGF-1R) on the cell surface [39] [41].

IF interferes with IGF-1 secretion by reducing the expression of IGF-1 receptors on the cell surface. IF has been shown to have a positive impact on reducing the expression of IGF-1 receptors, which reduces the capacity for IGF-1 signaling [42]. This mechanism is thought to be a part of the body's adaptation to periods of nutrient scarcity, where cellular proliferation is minimized to conserve energy. Another referred concept it that, IF is reported to increase the production of IGFBPs, which bind to free IGF-1 in the bloodstream, reducing its bioavailability to bind to IGF-1 receptors [41] [42]. One of the functions of IGFBPs is to inhibit the interaction of IGF-1 with its receptors by binding to it and preventing the activation of downstream signaling pathways. Another theory is that during IF, the body depletes glycogen stores, switches to fat metabolism, and produces ketones as an alternative energy source. Ketones are not only a cleaner energy source (producing fewer OS), but they also play a role in reducing IGF-1 production and the subsequent blocking of signaling pathways [10].

The Ras/MAPK (Ras/mitogen-activated protein kinase) pathway plays a critical role in cell proliferation, differentiation, and migration. In cancer, this pathway is often hyperactivated, promoting tumor growth and metastasis [43]. This signaling begins when IGF-1 primarily exerts its effects by binding to the IGF-1 receptor (IGF-1R) on the cell surface. The receptor is a tyrosine kinase which upon IGF-1 binding, it autophosphorylates, activating Grb2 and Sos, which are proteins that facilitate the conversion of inactive Ras (GDP-bound) to its active form (GTP-bound) [43] [44]. Once Ras is activated, it phosphorylates Raf, a MAP kinase, which later activates MEK, and this is how the MAPK/ERK signaling cascade is initiated [45]. The inhibitory process during IF, where IGF-1 levels are reduced, and the downstream activation of the Ras/MAPK pathway are also reduced. Downregulation of IGF-1 expression results in reduced Ras activation, thereby limiting the entire Ras/MAPK signaling cascade [46]. Decreased ERK phosphorylation implies reduced transcriptional activation of genes involved in cell proliferation and survival. Another inhibitory effect is the inhibitory effect of IF on OS through ROS, by lowering OS production leads to the inhibition of the hyperactivation of Ras/MAPK, thereby suppressing processes such as the epithelial-mesenchymal

transition (EMT), which is a key step in metastasis [47] [48].

The PI3K/AKT/mTOR pathway is an intracellular signaling pathway that is important in regulating cell survival, growth, and metabolism. In many cancers, this pathway is dysregulated due to the overproduction of OS, which promotes tumor cell survival and metastasis by enhancing resistance to apoptosis, facilitating angiogenesis, and increasing cell motility [47]. Activation of this pathway is initiated when there is overproduction of IGF-1, which leads to binding to IGF-1R. This binding triggers the autophosphorylation of the receptor and IRS-1 (insulin receptor substrate 1) and subsequent activation of phosphoinositide 3-kinase (PI3K) [49]. PI3K converts PIP2 (phosphatidylinositol 4,5-bisphosphate) to PIP3 (phosphatidylinositol 3,4,5-trisphosphate). PIP3 serves as a docking site for signaling proteins, such as AKT (also known as Protein Kinase B) [50]. Activated AKT migrates to the cell membrane, where it promotes cell survival and growth by phosphorylating mammalian target of rapamycin (mTOR), a major regulator of protein synthesis and cell proliferation. mTOR exists in two complexes, mTORC1 and mTORC2 [51]. AKT primarily activates mTORC1, which drives protein synthesis and cell growth. IF reduces insulin and IGF-1 levels, which leads to decreased activation of IGF-1R, prevents the activation of PI3K, and blocks the conversion of PIP2 to PIP3, leading to diminished AKT activation. Diminished AKT production downregulates mTOR, resulting in reduced protein synthesis, cell growth, and proliferation. The inhibitory effect of this pathway increases the susceptibility of cancer cells to apoptosis and reduces their metastatic potential [50] [52].

Wnt/β-catenin pathway is critical for regulating cell proliferation and differentiation. Aberrant activation of this pathway starts when there is an overproduction of OS, promotes metastasis by enhancing cancer stem cell characteristics, and supports EMT [53]. In the hyperglycemic state, Elevated ROS production leads to increased activation of IGF-1 and IGF-1R, leading to the activation of Wnt/β-catenin signaling, further driving cancer cell migration and invasion [54]. Indeed, evidence has verified sophisticated crosstalk between Wnt/β-catenin, OS, and IGF-1R signaling in different types of cell and biological processes. Activation starts when there is stimulation of IGF-1 due to high OS levels in the hyperglycemic state, where acetylation of β-catenin is induced through p300, which facilitates the formation of the LEF1–β-catenin complex [55]. This complex enters the nucleus and activates WNT target genes, thereby promoting tumor growth. Furthermore, overproduction of IGF-1 leads to inhibition of sirtuin (SIRT1) activity, which is responsible for preventing LEF1–β-catenin complex formation by deacetylating β-catenin [54]. In this case, by inhibiting sirtuin, IGF-1 overexpression promoted β-catenin nuclear retention and gene activation. The combination of IGF-1 and WNT signaling thus amplifies oncogenic potential by maintaining β-catenin in the nucleus, linking hyperglycemia to cancer progression and metastasis [56]. IF reduces OS, subsequently downregulates the Wnt/β-catenin pathway, and increases the expression of SIRT1, which in turn prevents the formation

of LEF1 the β-catenin complex, a major activator of this signaling. This reduction in pathway activity inhibits EMT and stemness, which are two crucial factors in cancer metastasis [57] [58].

Among the many bioactive molecules released by tumor cells, the HGF/c-Met pathway plays a crucial role in cell motility, invasion, and angiogenesis, all of which are critical for metastasis [59]. OS-IGF-1 interaction tigers the binding of HGF to its receptor tyrosine kinase c-MET, which triggers the activation of multiple downstream signaling pathways, which contribute to proliferation, growth, migration, survival, angiogenesis, invasion, and metastasis [60]. The interaction started when IGF-1 increased the expression of the c-Met receptor, which facilitated the binding of HGF to the receptors. When HGF binds to the c-MET receptor, it induces receptor dimerization and autophosphorylation at tyrosine residues Y1234 and Y1235, which initiate downstream signaling [61]. This activates pathways such as PI3K/AKT, MAPK/ERK, and STAT3, promoting cellular functions such as proliferation, migration, and survival [61] [62]. Additionally, the phosphorylation of Y1349 and Y1356 creates docking sites for adapter molecules (e.g., GAB1 and GRB2), further amplifying these signals [63] [64]. GAB1 acts as a scaffold protein that, upon phosphorylation, activates PI3K, contributing to processes such as epithelial-to-mesenchymal transition (EMT) in cancer cells, whereas GRB2 activates the RAS/MAPK pathway by binding to phosphorylated c-MET through its SH2 domain [59]. It forms a complex with SOS, a guanine nucleotide exchange factor that activates the RAS and triggers the MAPK cascade. This pathway is important for regulating cell proliferation, differentiation, and survival [60].

IF downregulates the HGF/c-Met pathway via several molecular mechanisms. First, IF lowers circulating levels of OS and growth factors, such as IGF-1, which are key activators of pathways shared with the HGF/c-MET axis, such as PI3K/AKT and MAPK/ERK [65]. The decreased availability of OS and growth factors reduces the activation potential of c-MET, indirectly downregulating it signaling [66]. IF leads to the activation of SIRT1, an NAD+-dependent deacetylase that plays a key role in cellular energy regulation [67]. SIRT1 interfere with the stability of the GAB1 and GRB2 adapter proteins that are crucial for propagating HGF/c-MET signals by inhibiting this pathway, IF reduces cancer cell motility and invasion, thereby hindering the metastatic spread of cancer cells [68] [69].

4. In Summary

Despite the need for more clinical research to validate the long-term benefits of IF in patients with cancer, the molecular mechanisms indicate that it has the potential to enhance cancer treatment outcomes. By targeting these pathways, IF could provide a complementary approach to conventional cancer therapies, maximizing their effectiveness while minimizing their adverse effects. Therefore, IF remains an appealing research focus owing to its cost-effectiveness, minimal side effects, and broad applicability across various tumor types.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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