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THEMATIC REVIEW

Nutrition, GH/IGF-1 signaling, and cancer

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Abstract

Cancer is the second leading cause of death in the United States and among the most prevalent diseases globally, with an incidence expected to grow because of smoking, pollution, poor dietary habits, obesity, and the rise in the older population. Given their ability to reduce risk factors, albeit with varying efficacy, nutrition and fasting could help prevent cancer and other age-related disorders. Calorie restriction (CR), various forms of intermittent fasting (IF) or periodic fasting (PF), and fasting-mimicking diets (FMDs) have been shown to improve health span, increase lifespan, and prevent or postpone cancer in rodents. The effects of specific diets and fasting regimens on aging and cancer appear to be mediated in part by the reduction in the activity of the growth hormone (GH)/insulin-like-growth-factor-I (IGF-1) axis. Nevertheless, recent data indicate that the alternation of low and normal levels of these hormones and factors may be ideal for optimizing longevity and function. Here, we review the role of nutrition, CR, and fasting/FMD on cancer, focusing on the hypothesis that the modulation of GH, IGF-1, and insulin signaling partly mediates the effect of these dietary interventions on cancer prevention.

Introduction

Nutrition and nutrient signaling play a central role in cancer biology. Cancer cells rely on growth factors, glucose, and many nutrients to guide function and to meet their metabolic needs, which can be remarkably different between various cancer types, and even within the same cancer selected at different stages of its progression. By limiting nutrient availability and energy, calorie restriction (CR) (which commonly refers to a 20–40% reduction in calorie intake) and various fasting and fasting-mimicking regimens (such as periodic fasting-mimicking diets or FMDs) induce healthy cells to switch from a proliferative to a maintenance, more highly protected state. In contrast, cancer cells are, by definition, unable to adapt to these non-growth conditions. When exposed to fasting conditions, they exhibit distinct responses known as differential stress resistance (DSR) (Raffaghello *et al.* 2008) and differential stress sensitization (DSS) (Buono & Longo 2018). DSR refers to the effects of fasting/FMD in increasing stress resistance in normal but not cancer cells, whereas DSS refers to a separate set of mechanisms that not only do not protect cancer cells but render them, but not normal cells, sensitive to a variety of cancer treatments (Di Biase & Longo 2016). For these reasons, they can make cancer cells more sensitive to chemotherapy, hormone therapy, radiation, immunotherapy, kinase inhibitors, and other treatments, as seen in several preclinical studies in cell line and mouse models of cancer, as well as in initial trials involving human subjects (Lee *et al.* 2012, Safdie *et al.* 2012, Caffa *et al.* 2015, de Groot *et al.* 2019, Caffa *et al.* 2020, de Groot *et al.* 2020, Di Tano *et al.* 2020, Cortellino *et al.* 2022, Ligorio *et al.* 2022). These effects of fasting/FMD on normal and cancer cells are mediated at least in part by the reduction in growth hormone (GH) and insulin-like-growth-factor-I (IGF-1) signaling. Chronic CR can also affect GH and IGF-1 signaling, the

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protection of normal cells, and the sensitization of cancer cells; however, its use in both mice and humans is limited by: 1) its unavoidable effect on weight and muscle loss and potential weakening of some immune functions (Park *et al.* 2017); 2) its burden on cancer patients who are already under stressful conditions and have often lost or are prone to losing weight and muscle mass; 3) its reduced effect compared to fasting/FMD on glucose, GH, IGF-1, insulin, and other factors, whose strong modulation is in most cases required in combination with cancer therapy to achieve strong anti-cancer effects or cancer-free survival (Salvadori *et al.* 2021).

GH is the primary regulator of circulating IGF-1, and the liver is its major producer. In turn, pituitary GH release is under the control of circulating IGF-1 through a negative feedback loop mechanism (Steyn *et al.* 2016). Both levels are finely balanced by mutual regulation during the different stages of life. Pituitary GH secretion and IGF-1 production by the liver and other tissues are also regulated by other hormones and mediators such as ghrelin, insulin, adipokines, free fatty acids (FFA), estrogen, thyroid hormones, and glucocorticoids whose production depends on food intake and energy balance (Vazquez-Borrego *et al.* 2018).

The close relationship between the endocrine system and nutrient availability explains how nutritional interventions and caloric intake may affect the metabolic processes of both healthy and cancer cells.

The notion that diet can influence cancer therapy has attracted significant interest, and many interventions are being tested to improve patients' quality of life and survival (Tajan & Vousden 2020). Accordingly, since downregulation of IGF-1 signaling has been associated with extended lifespan (Coschigano *et al.* 2000, Holzenberger *et al.* 2003, Chhabra *et al.* 2011, Bartke *et al.* 2013, List *et al.* 2019) and reduced cancer incidence (Ikeno *et al.* 2009, Levine *et al.* 2014), there has been a significant effort to identify pharmacological and dietary strategies to reduce GH and IGF-1 signaling (Kopchick *et al.* 2002, Klement & Fink 2016). However, the complexity of the crosstalk between them requires further investigation to understand how nutrients regulate GH and IGF-1 signaling, and how these factors determine lifespan and affect pathologies. On this basis, in this review, we will focus on nutrition, fasting/FMD cycles, and the GH/IGF-1 axis, with a particular focus on cancer prevention.

Nutritional regulation of the GH/IGF-1 axis

Nutrition plays a crucial role in modulating hormone levels, and the consumption of various nutrients has been associated with increased production of GH and IGF-1 (Thissen *et al.* 1994, Caputo *et al.* 2021) (Fig. 1). For instance, under conditions of high energy intake, the GH-dependent anabolic effects, coupled with the synergistic action of insulin, activate cellular processes related to protein synthesis to promote somatic growth. On the contrary, during energy deprivation, GH favors catabolic mechanisms, switching the metabolism from carbohydrate oxidation to lipolysis to preserve protein storage (Moller & Jorgensen 2009, Bartke & Darcy 2017). Remarkably, under different nutritional situations, GH stimulates IGF-1 and IGF binding proteins (IGFBPs) production, promoting metabolic functions with synergistic and opposing actions (Kaplan & Cohen 2007, Moller & Jorgensen 2009).

Before discussing how different nutritional approaches can influence the GH/IGF-1 endocrine axis, it should be emphasized that GH and IGF-1 levels vary physiologically over life, and their modulation can have different impacts on overall health in different age ranges.

After reaching adulthood, circulating GH and IGF-1 levels decline steadily, reaching low levels in the elderly, which can vary based on gender, exercise, and changes in body composition (Hartman *et al.* 1993, Moller & Jorgensen 2009, Junnila *et al.* 2013). This phenomenon, known as 'somatopause', may be a protective adaptation to aging, or possibly simply the consequence of age-related dysfunction. Of note, some human studies showed the efficacy of GH replacement therapy in improving lean and fat mass ratio, lipid profile, frailty, and sarcopenia in the late stage of life (Maison *et al.* 2004, Bitti *et al.* 2021) but it is not clear whether these benefits are effective only in subjects with low GH activity at baseline. Therefore, it is crucial to understand how nutrients influence GH-dependent effects during the different stages of life so that nutrition or pharmacological interventions can be modified and personalized to affect the levels of key growth factors and reduce tumor incidence without increasing frailty (Boguszewski & Boguszewski 2019).

Fasting and growth factors

In rodent models, PF and FMD protect against cancer and aging risk factors by regulating nutrient-sensing pathways, including GH/IGF-1 signaling. PF and FMD are emerging as feasible interventions that are viable for a large portion of the population and capable of achieving much stronger acute metabolic effects than CR while minimizing the side effects and burden of CR. CR can decrease plasma glucose, insulin, cholesterol, triglycerides, inflammatory cytokines, and, in mice, decrease IGF-1 levels by up to 25–30% (Matsuzaki *et al.* 2001, Mahoney *et al.* 2006). However, CR does not reduce IGF-1 levels in humans unless it is combined with protein restriction (Fontana *et al.* 2008).

Water-only fasting is the most extreme of dietary restrictions as it involves the complete elimination of nutrients and calories in the diet. Short-term frequent periods of fasting (12–24 h daily or several times a week)

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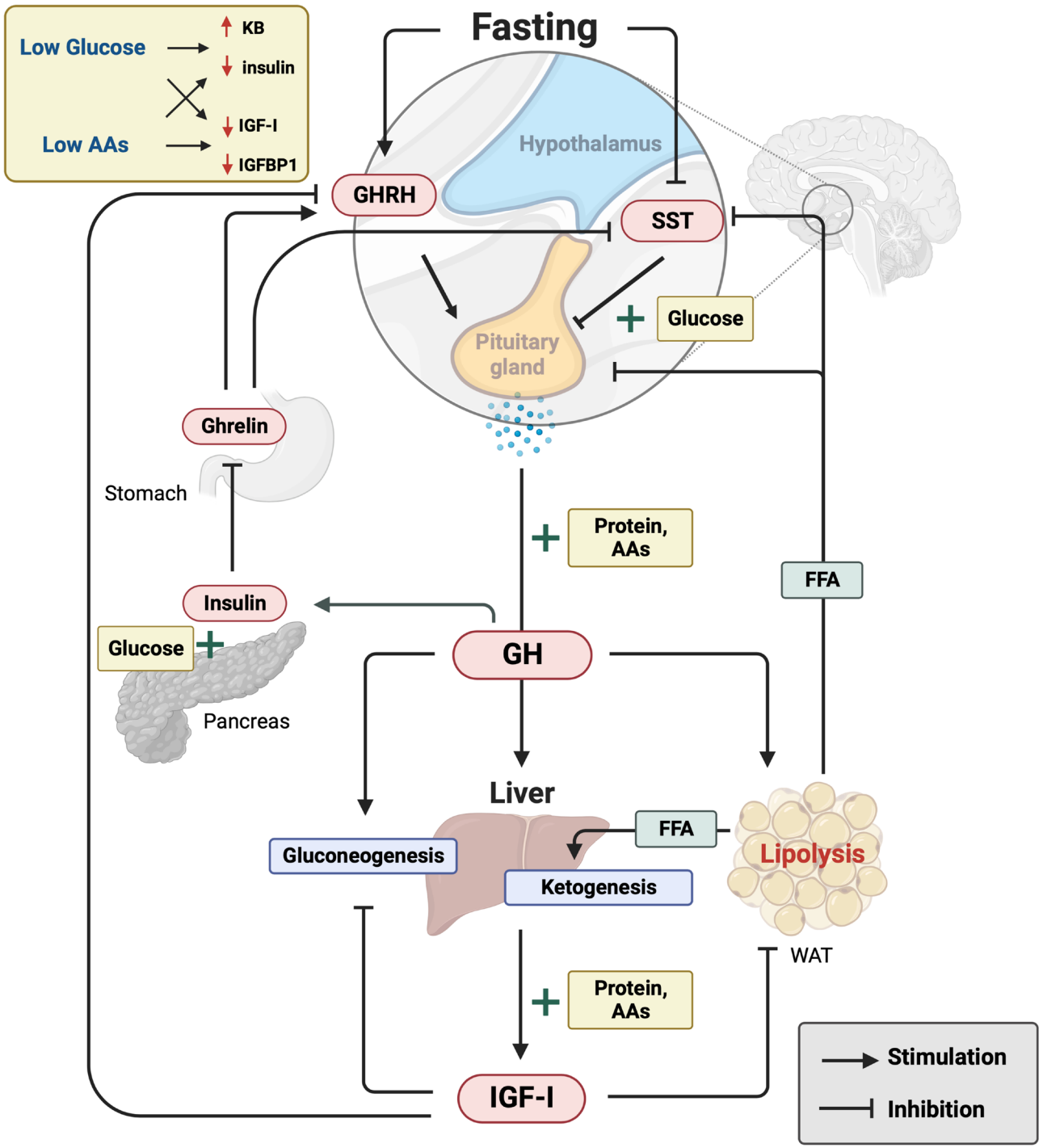

Figure 1

Schematic representation of GH/IGF-1 axis and nutrient regulation. GHRH, growth hormone release hormone; SST, somatostatin; GH, growth hormone; IGF-1, insulin-like growth factor I; FFA, free fatty acids; AAs, amino acids; KB, ketone bodies. Adapted from "Overview of hypothalamic and anterior pituitary hormones", by BioRender.com (2023).

are referred to as intermittent fasting (IF), while less frequent but more extended periods are known as PF (2 or more days 1–2 times a month or less) (Trepanowski *et al.* 2011, Longo & Mattson 2014). The significant differences between IF and PF are, in fact, the duration and frequency of the fast. There are multiple examples of IF plans, but the major method of IF in humans, entails 12–20 h of water-only intake daily, also known as time-

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restricted eating, an alternation of fasting and feeding days (alternate-day fasting), or several days of fasting per week (5:2 diets). In humans, PF cycles normally refer to 4–7 days of fasting or a fasting-mimicking diet, which can be reduced to as short as 1–2 days or as long as 5 days in mice depending on the severity of the fasting diet composition (Raffaghello *et al.* 2008, Brandhorst *et al.* 2015). IF and PF have different effects on various growth factors and metabolic markers, with IF causing more frequent but less pronounced changes than PF. Among the PF programs, the FMD has been developed to mimic many metabolic effects caused by water-only fasting but with reduced risk of malnutrition and burden, and possibly increased efficacy (Brandhorst *et al.* 2015, Wei *et al.* 2017, Caffa *et al.* 2020, de Groot *et al.* 2020). FMD is a plant-based caloric-restricted dietary regimen (typically between 300 and 1100 kcal per day) characterized by low proteins, sugars, and relatively high unsaturated fats. In mice, cycles of a 4-day FMD have been shown to lower blood glucose levels by 40% and IGF-1 by 45% while causing a many fold increase in ketone bodies and IGFBP-1, which inhibits IGF-1, by the end of the FMD (Brandhorst *et al.* 2015). These FMD cycles adopted twice a month starting in middle age extend health span and longevity, reduce visceral fat and skin lesions, promote hippocampal neurogenesis, rejuvenate the immune cells profile, and delay bone mineral density loss in mice (Brandhorst *et al.* 2015). Remarkably, these bi-monthly FMD cycles started in middle age reduce tumor incidence and delay cancer onset. In a pilot clinical trial, three cycles of a 5-day FMD decreased risk factors for aging, diabetes, cardiovascular disease, and cancer without significant adverse effects, supporting the use of FMDs to promote health span (Brandhorst *et al.* 2015). In this study, fasting blood glucose was decreased by 11.3%, circulating IGF-1 was decreased by ~24%, and IGFBP-1 increased by 1.5. Remarkably, glucose and IGF-1 remained lower than baseline levels, respectively, by ~6% and ~15%, even after resuming their regular diet for 5–7 days following the last FMD cycle. Since then, numerous clinical trials conducted on patients suffering from different types of cancers have demonstrated their feasibility and potential efficacy in combination with various anti-cancer drugs (Nencioni *et al.* 2018, Caffa *et al.* 2020, de Groot *et al.* 2020).

After prolonged fasting, the serum level of IGF-1 decreases, causing impaired IGF-1 negative feedback action on GH and its increased circulation (Vance *et al.* 1992, Hartman *et al.* 1993). Despite increased GH secretion, 5 days of PF in humans decreases IGF-1 levels by up to 65% (Ketelslegers *et al.* 1995, Maccario *et al.* 2001, Moller & Jorgensen 2009). This effect is favored by a five-fold increase in IGFBP-1 which, by binding circulating IGF-1 and reducing its bioavailability, in turn compromises feedback inhibition of IGF-1-dependent GH secretion (Zapf *et al.* 1995). This aligns with findings from mice studies where 24–72 h of PF decreases IGF-1 levels by 70% while increasing IGFBP-1 by 11-fold (Frystyk *et al.* 1999, Lee *et al.* 2010). This metabolic rearrangement is associated with reduced protein synthesis and downregulation of the PI3K/AKT and mTOR/S6K pathways (Imae *et al.* 2003, Sans *et al.* 2004). In these circumstances, low insulin levels, induced by the fasting state, contribute to GH resistance by reducing the expression of GHR in the liver (Aimaretti *et al.* 1999). IGF-1 production might also be limited by mechanisms downstream of the GH receptor, such as signal transducer and activator of transcription 5 (STAT5) inhibition induced by fibroblast growth factor-21, whose upregulation may occur also in states of nutritional deprivation (Inagaki *et al.* 2008, Fazeli & Klibanski 2014). Notably, because in short-term fasting GH secretion is increased without significantly affecting IGF-1 levels, the hypothalamic increased frequency of growth hormone release hormone (GHRH) production, and longer and more pronounced periods of somatostatin (SST) discontinuation are believed to drive the early effects of fasting on GH signaling regardless of the modulatory mechanism dependent on IGF-1 levels (Hartman *et al.* 1992). Conversely, refeeding after either short-term fasting or recovery from chronic food restriction is followed by a quick response that returns GH and IGF-1 levels to normal (Counts *et al.* 1992, Argente *et al.* 1997).

Interestingly, adult patients with either GH deficiency (GHD) or acromegaly show atypical GH levels in response to nutritional deprivation (Ho *et al.* 1992), proving that fasting depends on lowering GH signaling to exert its effects. In normal healthy subjects, on the contrary, the significant increase in food intake suppresses GH secretion before changing body composition (Cornford *et al.* 2011). The inhibition of GH release may be due to different mechanisms, including increased FFA availability (Casanueva *et al.* 1987), perturbation in GHRH and SST secretion (Vance *et al.* 1992), modification of IGF-1 availability IGFBP-dependent (Maccario *et al.* 2001), and hyperinsulinemia (Cornford *et al.* 2011). Notably, these mechanisms associated with aging- and obesity-related alterations in the GH/IGF-1 axis may favor an early onset of the 'somatopause' phenotype (Steyn *et al.* 2013).

Energy intake has indeed been proven to be decisive in modulating the GH/IGF-1 axis, even if these effects may also depend on the contributions of individual macronutrients.

Protein, amino acids, growth factors, and cancer

Proteins and specific amino acids (AAs) are central regulators of GH and IGF-1 levels. It is well-established that high protein levels in the diet can promote an increase in IGF-1, and this association appears to be supported more by animal proteins (Fontana *et al.* 2008, Levine *et al.* 2014).

Recent findings from the Nurses' Health Study and Health Professionals Follow-up Study on a population

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of 14709 adults have confirmed that high animal protein intake was positively associated with IGF-1 and inversely associated with IGFBP-1 and IGFBP-2, which are crucial in modulating IGF-1 activity (Lee *et al.* 2022). In the same population, higher consumption of plant-based protein still positively correlated with IGF-1 but also with IGFBP-1, while substituting plant protein with animal protein was associated with reduced IGFBP-1. Of note, the negative correlation between IGF-1 and IGFBPs was maintained only in individuals who had unhealthy behaviors (e.g., alcohol consumption, smoking, obesity, and physical inactivity) suggesting that other factors can affect IGF-1 signaling.

However, the evaluation of circulating IGF-1 and IGFBP-1 in vegans revealed that they were respectively lower and higher than in non-vegans (Allen *et al.* 2002), highlighting the stronger impact of animal proteins compared to plant-based ones on this pathway.

A previous study by Levine *et al.* (2014) examined the link between protein intake and mortality. The analysis considered different intakes (high, moderate, and low) and sources (animal and plant-based) of proteins in a population including 6381 adults over 50. Findings from this study showed that subjects aged 50–65 having high protein intake (~20% of calories from protein) and moderate intake (~19–10% of calories from protein) had a four-fold and three-fold increase in cancer incidence compared to those on a low protein diet (below 10% of calories from protein) during an 18 year follow up period. In contrast, in subjects over age 65, moderate or high protein intake was associated with reduced cancer incidence and overall mortality, implying that the modulation of the GH/IGF-1 axis might have a different impact at different stages of life. It is possible that, in the over-65 population, the group reporting a low or very low protein intake includes a portion of malnourished, frail, and sick individuals, which may partly explain the higher mortality risk.

In line with data from the human population, studies on mouse models of melanoma and breast cancer on high (18%) or low (4–7%) protein diets have shown that high protein intake and IGF-1 promoted cancer generation and progression, whereas severe protein restriction caused severe weight loss in old but not young mice (Levine *et al.* 2014). Interestingly, these associations in humans were either abolished or reduced if the protein source was plant-based.

While this section focuses exclusively on the role of proteins, it is important to consider that the quality of food and other nutrients may also affect IGF-1 signaling and health.

Sources of high animal protein, including red meat, processed meat, poultry, lean fish, eggs, and dairy products, are considered to have high insulinemic potential (Tabung *et al.* 2016) and tend to be more adversely associated with biomarkers of insulin and the IGF axis compared to non-meat animal protein (Lee *et al.* 2022). Insulin resistance and hyperinsulinemia are known to be risk factors for chronic diseases, including cancer. Consistent with this, it is plausible that diets rich in high animal protein with insulinemic potential are associated not only with an increased risk of type 2 diabetes but also with colorectal cancer and multiple myeloma (Tabung *et al.* 2018, Lee *et al.* 2019).

The robust epidemiological evidence that high animal protein consumption increases serum IGF-1 levels in humans (Crowe *et al.* 2009, Rahmani *et al.* 2022) also explains its effects on linear growth (Hoppe *et al.* 2006). Furthermore, as milk and casein consumption increase circulating IGF-1 (Crowe *et al.* 2009, Tucker *et al.* 2015), excessive milk intake has been investigated and associated with liver and breast cancers, and possibly lymphoma, in adult Chinese populations (Kakkoura *et al.* 2022). However, the relationship between dairy consumption and cancer risk remains controversial.

Due to the correlation between high protein consumption and cancer, a direct action of specific amino acids on pathways linked to cancer cannot be excluded.

Therefore, many studies have focused their attention on the dietary manipulation of specific AAs present in significant amounts in animal proteins. In general, mammalian cells cannot synthesize essential amino acids (EAAs), so both normal and cancer cells depend on their dietary availability. By contrast, normal cells can synthesize nonessential amino acids (NEAAs) and usually do not depend on a dietary supply of these amino acids. Notably, some tumors have shown increased demand for NEAAs for growth and survival, making NEAAs a potential target for cancer cells. The concentration of EAAs in the diet can also impact tumor processes. For example, the combination of high consumption of leucine, isoleucine, and valine, known as branched-chain amino acids (BCAAs), and a high-fat diet is associated with obesity and insulin resistance, which can promote the growth of insulin-sensitive tumors (Newgard *et al.* 2009). In addition, BCAAs increase serum IGF-1 levels in humans (Li *et al.* 2015) and are involved in the early events of pancreas cancer development (Mayers *et al.* 2014). Preclinical studies indicate that dietary limitation of EAAs contrasts the development of insulin resistance in obese mice fed a high-fat and high-sugar diet (Cummings *et al.* 2018) and may impact cancer development (Ananieva & Wilkinson 2018).

Restriction of EAAs methionine or tryptophan has been demonstrated to decrease IGF-1 and promote health (McCarty *et al.* 2009, Orgeron *et al.* 2014). Methionine can play a central role in regulating growth factor levels and health. Mammalian cells rely on the diet for methionine supply but can produce it from homocysteine or methylthioadenosine. While the presence of homocysteine facilitates the growth of normal cells under methionine-restricted conditions, certain cancer cells, like the Walker-256 carcinosarcoma, are incapable of surviving under conditions of limited

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availability of this particular amino acid (Cavuoto & Fenech 2012). The inability of some cancer cells to survive without methionine is not entirely understood, but it is presumably related to defects in some molecules crucial for methionine metabolism (Chaturvedi *et al.* 2018). The interest in the dietary restriction of sulfur AA as an antitumoral strategy was proposed a long time ago, and its efficacy has been confirmed in several preclinical studies in mouse models of cancers (Komninou *et al.* 2006, Sinha *et al.* 2014, Jeon *et al.* 2016). However, limiting their availability using drugs or removing them from the diet represents an anticancer intervention with limitations since normal cells also require these amino acids.

Carbohydrates, fats, and growth factors

The altered glucose metabolism in cancer cells often depends on high glucose uptake (Cairns *et al.* 2011). The actions of GH/IGF-1 on carbohydrate and lipid metabolism are closely connected. Under normal conditions, GH stimulates insulin release and glucose metabolism, lowering glycemia. Some data suggest that IGF-1 production, under GH control, requires adequate insulin activity (Chiarelli *et al.*, 2004). Moreover, one of the main functions attributed to GH is its significant lipolytic action, which may result in a reduction in body fat mass and FFA release into circulation. In turn, FFAs have an inhibitory effect on GH secretion. Of note, the rise in FFAs, dependent on overstimulation of GH, may cause an increase in insulin secretion and glucose resistance (Neely *et al.*, 1992). Along with the effect on lipolysis, GH controls the metabolism of triglyceride-rich VLDL and, hence, the availability of FFAs for peripheral tissues. In addition, GH promotes the expression of low-density lipoprotein receptors (Garg *et al.* 2011) and the production of high-density lipoprotein, lowering circulating cholesterol levels.

In this context, low carbohydrate ketogenic diets (KDs) have been tested to alter glucose availability to cancer cells and to test the effect of high-fat levels on cancer growth and survival. By reducing carbohydrates in favor of fat intake, dietary regimens like KDs can force the body to metabolize fat for energy. Unlike the high-fat and high-carbohydrate Western diet (WD), which is associated with obesity and increased cancer development, KDs can cause delayed cancer progression (Branco *et al.* 2016). The antitumoral properties of some KDs may be caused by the reduction of circulating glucose, insulin, and IGF-1, but effects on these factors can be limited compared to those caused by fasting (Nencioni *et al.* 2018, Klement 2019). To compensate for the glucose deficiency, the liver promotes beta-oxidation of FFAs and the production of ketone bodies (acetoacetate, b-hydroxybutyrate, and acetone) which are released in circulation to reach peripheral tissues. Interestingly, some studies revealed inverse associations between IGF-1 levels and β-hydroxybutyrate (Cohen *et al.* 2018, Klement *et al.* 2022). In agreement with these findings are the results from a recent systematic review and meta-analysis of controlled clinical trials on the efficacy of KDs as adjuvant therapy on cardiometabolic outcomes in patients with cancer. They found that KDs reduce glucose, IGF-1, triglycerides, body weight, BMI, and fat mass (Amanollahi *et al.* 2022).

However, another recent meta-analysis from ten controlled trials aimed to evaluate the effects of different KDs on patients suffering from several types of cancers offered a different perspective relative to IGF-1. Despite the low dietary compliance, KDs had a significant effect on the reduction of body weight and fat mass but no significant effect on blood glucose, insulin, and lipid profile except triglycerides. Above all, there were no significant changes in IGF-1 and TNF-α related to tumor growth (Zhao *et al.* 2022*a*). Notably, the growth of many cancer cell types can be stimulated by fatty acids and/or ketone bodies (Bonuccelli *et al.* 2010, Sperry *et al.* 2020), and different fat molecules can have opposite effects on cancer growth (Li *et al.* 2022), which may explain the inconsistent effects of KDs on cancer progression in mice and humans.

The conflicting outcomes from these analyses indicate that additional pre-clinical and clinical data are required to determine which cancers KD may be effective against, especially in combination with standard-of-care interventions.

The GH/IGF-1 axis and cancer

The hypothalamic-pituitary-somatotropic axis, through the hormonal activity of GH and IGF-1, regulates somatic growth, sexual maturation, maintenance of lean and bone mass, and many cell functions, including metabolism (Ernst & Rodan 1990, Sjogren *et al.* 1999, Lu *et al.* 2019).

The anterior pituitary gland releases GH in a pulsatile manner, characterized by nocturnal secretory episodes that cover about 70% of its daily production. These episodes are separated by diurnal intervals of relative secretory quiescence with undetectable GH levels in the blood (Ho *et al.* 1988, Pombo *et al.* 2001). This process is positively controlled by the GHRH and ghrelin (Dimaraki & Jaffe 2006, Khatib *et al.* 2014) and negatively regulated by the SST (Lu *et al.* 2019). After release, GH binding with the GH receptor (GHR), expressed in many tissues (Moller & Jorgensen 2009), results in a cascade of reactions that activate several pathways like JAK2-STAT5, MAPK-ERK1/2, PI3K-Akt-mTOR, and PLC/PKC/Ca2C (Zhu *et al.* 2001, Bocharov *et al.* 2018, Basu *et al.* 2019, Chhabra *et al.* 2019). GH signaling promotes transcription and synthesis of IGF-1, particularly in the liver, thus regulating its circulating levels (Guevara-Aguirre *et al.* 2018).

Similarly, by binding to the IGF-1 Receptor (Werner *et al.* 2000), IGF-1 triggers the activation of MAPK-ERK1/2, PI3K-Akt, and mTOR-S6K signaling (Yamauchi

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& Pessin 1994, Grey *et al.* 2003) which are involved in many cellular processes, including differentiation, proliferation, and apoptosis. As the name suggests, IGF-1 and insulin, as well as their respective receptors, exhibit high molecular and functional homology, which explains cross-effects on growth and metabolism (such as anabolic, lipotropic, and hypoglycemic actions) (Kaplan & Cohen 2007, Siddle 2011). In addition, both hormones may lead to the activation of the insulin receptor (IR). Curiously, IGF-1Rs are expressed in almost all cell types but not in hepatocytes. The free-circulating form drives the biological activity of IGF-1. It is regulated by a group of six different IGFBPs, produced by the liver under the influence of GH, that carry IGF-1 and modulate its function systemically (Baxter 2014, Bach 2015). The complex roles of IGFBPs include protecting IGF-1 from metabolic degradation but also exerting IGF-1-independent actions mediated mainly by different receptors (Cohen 2006). Because of its potent mitogenic and antiapoptotic activities, IGF-1 plays an essential role in growth, especially postnatal life. Thus, it is considered primarily responsible for the growth-promoting effects of GH (Resnicoff *et al.* 1995, Werner *et al.* 2000) but also plays a crucial role in cancer.

In breast cancer, the GH/IGF-1 axis has been shown to favor tumor development by influencing angiogenesis, stemness, and chemoresistance (Chen *et al.* 2015, Subramani *et al.* 2017), and the overexpression of IGF-1 and IGF-1R has been related to malignant progression and prognosis in human breast carcinomas (Gebre-Medhin *et al.* 2001, Wu *et al.* 2011). Such evidence is supported by a genome-wide association study showing GH-induced molecular pathways being highly associated with breast cancer susceptibility (Menashe *et al.* 2010).

Moreover, it has been shown that GH regulates several mechanisms that render tumors resistant to chemotherapy and other targeted therapies, such as increasing tumoral drug efflux via ABC transporters, inducing epithelial-to-mesenchymal transition (EMT), suppressing apoptosis, increasing cancer stem cells (CSCs), and inducing fibrosis and extracellular matrix (ECM) remodeling (Basu & Kopchick 2019). This is a crucial aspect to consider, as the development of drug resistance is a major limitation for current standard therapies, primarily chemotherapy.

Recent studies highlight the significant role of GH inhibition in anticancer therapies for melanoma and HCC, both tumors associated with marked drug resistance. Preclinical experiments on GHR antagonist (GHRA) mice transgenic for a murine GHR antagonist (G119K bGH) show that circulating GHRA significantly suppresses melanoma implantations and increases tumor sensitivity to cisplatin treatment compared to that of WT mice. Similarly, in HCC, which normally expresses higher levels of GHR than normal liver hepatocytes, GHRA sensitizes tumors to sorafenib, the current standard care therapy for hepatocellular carcinoma (HCC). GHRA not only directly inhibits the action of GH but also reduces the supply of IGF-1 to tumor cells. Remarkably, the cumulative effect of GHR inhibition and lower IGF-1 levels induced by the combination of GHRA and chemotherapy leads to marked tumor suppression and, in some cases, even complete remission (Basu *et al.* 2022).

For these reasons, the GH/IGF-1 axis emerged as a promising target for cancer treatments and prevention aimed at inhibiting cell proliferation by down-regulating IGF-1 (Chitnis *et al.* 2014, Werner *et al.* 2019). However, a recent meta-analysis on the correlation between IGF-1 levels and all-cause mortality conducted on 19 studies involving 30 876 subjects indicates that IGF-1 values that are either too low or too high can both be associated with an increased risk of mortality (Rahmani *et al.* 2022). More importantly, a specific mid-range of 120–160 ng/mL has been identified as associated with the lowest mortality risk. Furthermore, the same study showed a positive correlation between the intake of animal proteins, carbohydrates, and dairy products with high IGF-1 levels, emphasizing how specific dietary restrictions have the potential to reduce mortality by optimizing the level and activity of IGF-1 and other growth factors and pathways. In this regard, evidence deriving from congenital disorders affecting this signal (Fig. 2) led to more conclusive but still controversial conclusions regarding the role of the GH/IGF-1 axis in cancer, as will be discussed in the following paragraphs.

GH, IGF-1, and cancer: mouse studies

Several genetic mouse lines have been generated to characterize the role of GH and IGF-1, offering evidence for their link to DNA damage and cancer. Among these mouse models, Snell dwarf mice display pituitary hypoplasia that leads to the improper formation and dysfunction of prolactin (PRL), thyroid-stimulating hormone (TSH), and GH (Li *et al.* 1990) which results in very low levels of circulating IGF-1 (Brown-Borg & Bartke 2012). These mice are also protected from age-related diseases, including cancer (Vergara *et al.* 2004), showing an increased lifespan compared to WT mice (Flurkey *et al.* 2001, Dominick *et al.* 2015). As with Snell mice, Ames dwarf mice show similar GH and other deficiencies in the pituitary gland. They exhibit increased lifespan, high resistance to oxidative stress inducers, including paraquat (Bokov *et al.* 2009), and have a lower incidence of malignancies, showing ~35% reduction of lung adenocarcinoma incidence. Of note, fatal neoplastic diseases in Ames mice occur later in life compared with their normal siblings (Ikeno *et al.* 2003).

Moreover, $GH^{-/-}$ and $GHR^{-/-}$ mice (Laron Syndrome, LS), both display severe IGF-1 deficiency, smaller body size, in both length and weight (Zhou *et al.* 1997), and reduced incidence of certain types of cancer, particularly lymphomas and pulmonary adenomas/carcinomas, compared with wild-type mice (Wang *et al.* 2005, Ikeno *et al.* 2009, Duran-Ortiz *et al.* 2021). Finally, growth hormone receptor/-binding protein

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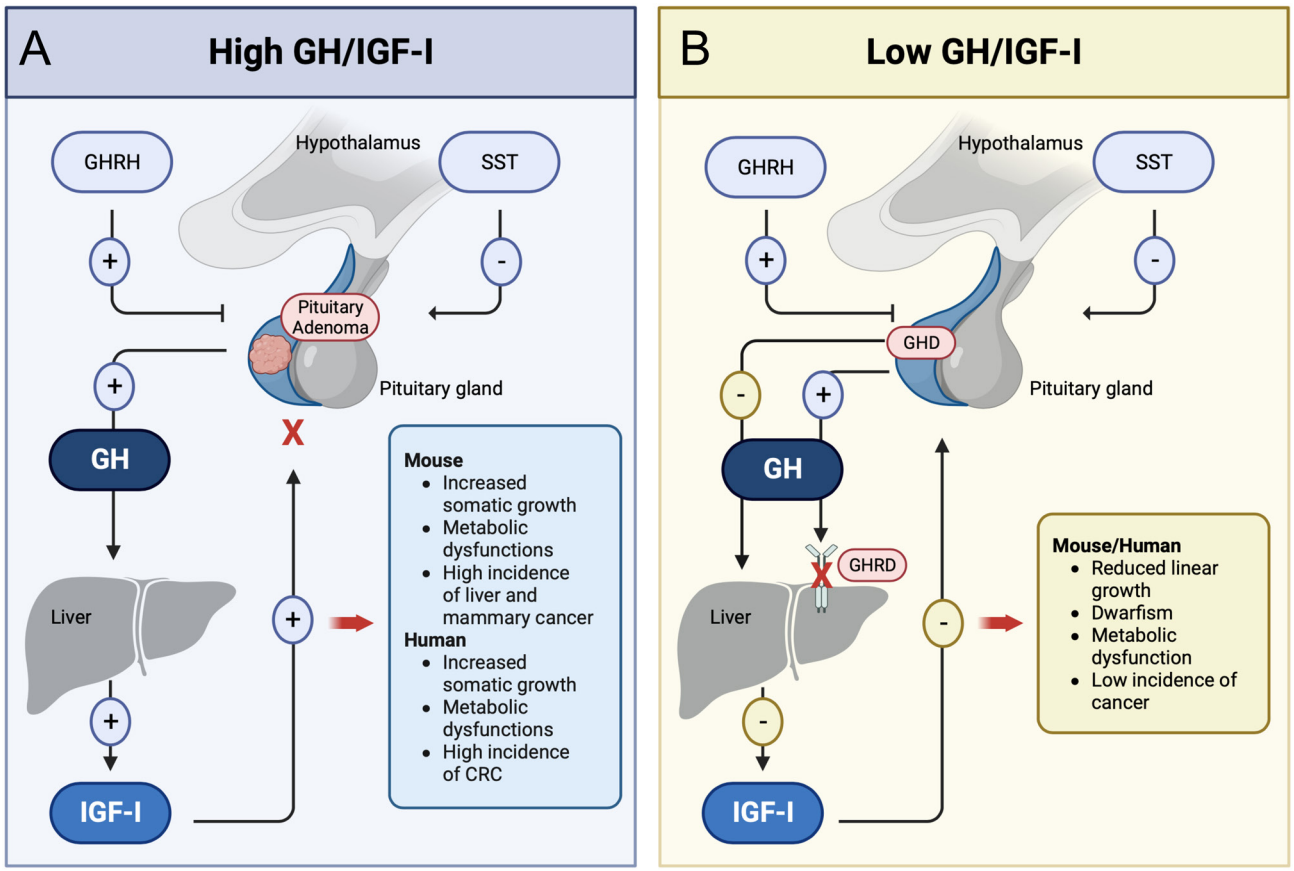

Figure 2

Alterations in the GH/IGF-1 signaling. Under physiological conditions, the anterior pituitary gland releases GH which, binding the GH receptor (GHR) in the liver, leads to IGF-1 secretion. (A) In pathological conditions such as acromegaly, the presence of a pituitary adenoma induces excessive secretion of GH by the pituitary gland. The consequent overproduction of IGF-1 causes abnormally high linear growth and metabolic dysfunctions. It also correlates with high colon rectal cancer (CRC) incidence. (B) As a result of a GH deficiency (pituitary dwarfism) or GHR mutation (Laron syndrome), the synthesis of IGF-1 is reduced in the liver and many other extrahepatic tissues. The abrogation of IGF-1 production impairs growth and affects IGF-1 function as a negative feedback regulator of GH secretion. It also correlates with a low incidence of cancer. Created with Biorender.com (2023).

$(GHR/BP)^{-/-}$ mice show a lower incidence and a delayed occurrence of neoplasia compared to WT mice, particularly lymphomas and pulmonary carcinomas (Ikeno *et al.* 2009).

When exploring the association between the GH/IGF-1 axis and cancer, it is equally important to examine the opposite condition, when the signal is overstimulated. GHRH transgenic mice and other GH overexpressing mice, which display increased serum levels of GH, PRL, and IGF-1, are indeed significantly larger in body size than WT mice (Moore *et al.* 1994) sharing many characteristics with acromegalic patients. They also exhibit accelerated somatic growth and early signs of aging, with a significant reduction in lifespan (Bartke 2003). Although they die prematurely mainly because of cardiovascular abnormalities (Izzard *et al.* 2009), in these mice, the chronic expression of GH and consequently high expression of IGF-1 results in a high incidence of tumors in the liver (Snibson *et al.* 2001, Miquet *et al.* 2013) and the mammary glands (Tornell *et al.* 1992).

Similarly, further experiments in rodents with impaired GH, GHR, or IGF-1 suggest that the GH/IGF-1 axis plays a key role in breast carcinogenesis in genetic and chemically induced hormone-dependent or independent models. Transgenic mice expressing the GH antagonist (GHA-tg) have reduced levels of IGF-1 and exhibit a lower incidence of tumors in the mammary gland relative to control mice after being treated with the carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) (Pollak *et al.* 2001). Accordingly, mice bearing MCF-7 xenografts treated with the GH antagonist Pegvisomant show a 70–80% decrease in circulating IGF-1 along with a 30% decrease in mammary tumor size (Divisova *et al.* 2006).

The intricate systemic interplay between GH/IGF-1 signaling and cancer has been thoroughly examined in a recent review by Marker *et al.*, which emphasizes its role in the promotion and progression of neoplasia in several genetic and chemical models of cancer in rodents (Marker *et al.* 2023). Multiple prostate cancer studies have shown the overexpression of GHR and circulating

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levels of IGF-1, both *in vitro* and *in vivo*, suggesting an important role of the GH/IGF-1 axis in tumor progression. Findings from studies on prostate cancer in the genetic mouse model of C3(1)/TAg crossed with GHR$^{-/-}$ further support the significance of GH actions by showing a correlation between reduced GH levels and decreased cancer progression (Wang *et al.* 2005). In a mouse model of diethylnitrosamine (van den Top *et al.* 2004) induced hepatocellular carcinoma (Zhao *et al.* 2022*b*), the GH/IGF-1 axis plays a crucial role in tumor formation (Zhao *et al.* 2022*b*). Indeed, experiments on liver cancer using mice with inactive GH receptors (lit/lit mutation) have shown suppression of tumor formation, indicating the necessity of GH/IGF-1 signaling in DEN-induced hepatic tumorigenesis. Conversely, in bGH mice that overexpress bovine GH, the same treatment with DEN induces 2.6 times and 4 times higher liver tumor formation in males and females, respectively, compared to age-matched controls (Basu & Kopchick 2019).

However, colorectal cancer (CRC) studies in rodent models with liver-specific IGF-1 deficiency (LID mice), in rats with a spontaneous mutation that inactivates the GH1 gene encoding GH, and in engineered mice with an inactivating mutation in the GHRH gene encoding for GHRH produced mixed results suggesting a more complex regulation potentially influenced by additional factors (Marker *et al.* 2023). Given this fact, the relationship between GH, IGF-1, and cancer progression needs to be further explored.

GH, IGF-1, and cancer: human studies

GH excess in humans is mainly associated with a condition known as acromegaly, which is caused by a GH-secreting pituitary adenoma (Chanson & Salenave 2008). Depending on the stage of life in which it occurs, it usually leads to gigantism (Eugster & Pescovitz 1999) or excess growth in extremities growth (hands, feet, face) and internal organs (Chanson & Salenave 2008). Because of the chronic over-secretion of GH, these individuals suffer from different comorbidities, such as insulin resistance, diabetes mellitus, and severe cardiac problems (Chanson & Salenave 2008). Notably, individuals with untreated acromegaly experience a higher mortality rate, with a reduced life expectancy of approximately ten years compared to the general population. While cardiovascular and respiratory complications are the primary cause of mortality in acromegaly, it should be noted that approximately 15% of reported deaths in acromegaly are attributable to malignancy (Chanson & Salenave 2008) with CRC showing an increased incidence in several studies (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016).

Importantly, pharmacological interventions aimed at normalizing IGF-1 levels, such as the treatments with somatostatin analogs or the FDA-approved GHR antagonist Pegvisomant, can reduce the mortality rate of acromegaly patients to that of the average population, supporting the role of excess IGF-1 in the increased risk of mortality in these patients (Ayuk & Sheppard 2008, Holdaway *et al.* 2008, Melmed 2009, Kopchick *et al.* 2014).

Congenital GH and IGF-1 deficiency may serve as a better model for understanding the relationship between these factors and cancer (Shevah & Laron 2007, Guevara-Aguirre *et al.* 2011, Steuerman *et al.* 2011). Growth hormone receptor deficiency (GHRD, Laron syndrome, LS) is generally characterized by very low circulating IGF-1 and elevated GH levels (Rosenfeld 2005). GH/IGF-1 deficiency may also occur due to a GHRH-receptor (GHRH-R) defect or GH gene deletion (Isolated GH deficiency, IGHD). Additionally, defects in post-GHR signaling and several disorders associated with reduced IGF-1 stability or availability may contribute to IGF-1 deficiency (Woods *et al.* 1996, Kofoed *et al.* 2003, Cohen *et al.* 2008, Argente *et al.* 2017). Notably, in individuals affected by LS, GHR dysfunction results in very low IGF-1 levels in serum, which induces the downregulation of the inhibitory feedback regulatory loop of GH release. Accordingly, circulating GH increases within the acromegalic range (Laron *et al.* 1966). LS patients exhibit a typical phenotype characterized by dwarfism and obesity. The only treatment that has proved effective in stimulating somatic growth and is remarkably safe is the administration of exogenous IGF-1 (Backeljauw *et al.* 2001). LS subjects are insulin-sensitive and protected from type 2 diabetes and cancer (Guevara-Aguirre *et al.* 2011), analogously to the observations in GHRD mice (Duran-Ortiz *et al.* 2021). These findings are also supported by an epidemiological analysis focused on the role of GH/IGF-1 in cancer in LS patients (Steuerman *et al.* 2011, Werner *et al.* 2020). This analysis surveyed the prevalence of malignancies in 538 patients with congenital IGF-1 deficiency from different cohorts, including LS, IGHD, GHRGH-R mutations, and multiple genetic pituitary hormone deficiencies (cMPHD). In this report, 752 first-degree family members and relatives were also included. Interestingly, none of the LS patients had developed a malignancy, even though many received IGF-1 or GH treatment. Instead, a low incidence of malignancy was reported among first-degree and further relatives with significant differences with the homozygote GHRD carriers. The same trend has been seen in the other cohorts, although rare cases of malignancy have been reported (Table 1). These results endorse the notion that individuals born with IGF1 deficiency are protected against cancer onset.

Moreover, genomic profiling of immortalized lymphoblastoid cell lines derived from LS patients identified several genes involved in pathways differentially expressed in samples of LS patients compared to age- and gender-matched controls (Lapkina-Gendler *et al.* 2016). These pathways include PI3K-AKT and Jak-STAT signaling, apoptosis, and metabolic processes. In addition, the analyses revealed that genes involved in managing the cell cycle, motility, and oncogenic transformation were mainly down-regulated

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Table 1 Prevalence of malignancy in patients with secondary congenital IGF-I deficiency and their relatives (data from Steuerman, Shevah & Laron 2011).

	Laron	IGHD	GHRH-R	cMPHD
Total number (n) homozygotes	260	116	79	113
Malignancies n of events	0	1	3	3
Total number (n) first-degree relatives	213	203	150	181
Malignancies n of events	18	7	0	6
Total number (n) further relatives	113	13	4	1
Malignancies n of events	25	4	1	1
Total number (n) siblings	86	96	6	86
Malignancies n of events	5	2	0	2

in LS-derived cell lines compared to control cell lines (Werner *et al.* 2020). These findings may represent the molecular signature for cancer protection in LS.

In summary, there is strong evidence linking the downregulation of GH/IGF-1 signaling to reduced cancer mortality. Similarly, overstimulation of GH and IGF-1 under 'favorable' circumstances, such as those supported by certain nutritional conditions, is believed to promote the occurrence of cancerous events by reducing DNA repair time during cell cycle progression and therefore increasing the risk of mutations that lead to the development of tumors (Boguszewski & Boguszewski 2019). Chemotherapy remains one of the most successful therapies in cancer treatment to date. However, despite the tremendous progress in the development of drugs aimed at specific molecular targets of tumors, cancer cells often develop resistance through alternative mechanisms, as mentioned before, that make therapies ineffective over time. A recent review by Basu and Kopchick discusses the correlation between elevated circulating levels of GH and IGF-1 and poorer responses in different types of tumors, implying the role of such factors and their interactions with GHR and IGF-1R receptors in promoting resistance to anticancer treatments (Basu & Kopchick 2019, Basu & Kopchick 2023).

CR, dietary restriction, and fasting regimens, in part by lowering IGF-1 levels, have been shown to be effective in improving responses in combination with current therapies. Therefore, to overcome problems related to resistance, preclinical and clinical efforts have been directed at understanding the interactions between GH and IGF-1 with key proteins in tumor cells, whether as a single therapy or in combination with current therapeutic options.

For these reasons, unlike the unexpected failure of IGF1R-targeted treatments, mainly due to adverse events, the use of GHR antagonists and inhibitors, such as pegvisomant, has provided excellent outcomes, thus offering a unique opportunity to explore the potential of GHR inhibition and the resulting modulation of IGF-1 levels as an adjuvant therapy to current therapies (Basu & Kopchick 2023). Further studies aimed at the implementation of GHR antagonists, possibly combined with nutritional plans providing a microenvironment hostile to tumor growth, and standard of care therapies, could prove capable of tumor regression and at the same time possibly reducing the dosage of drugs and associated side effects in patients.

IGF-1 and obesity in cancer

Just as CR and fasting cycles can decrease cancer incidence, overeating is associated with the opposite effect. In recent years, many studies have reported that obesity increases cancer incidence. A sedentary lifestyle and energy imbalance are factors that favor increased adipose mass, affecting the adipose tissue homeostasis and the production of adipose-derived mediators such as adiponectin, leptin, and other pro-inflammatory hormones and adipokines (such as TNF-α and IL-6) (Ouchi *et al.* 2011). Adipose tissue is an active endocrine organ that regulates lipid and glucose metabolism, insulin sensitivity, angiogenesis, inflammatory response, and many other processes (Sethi & Vidal-Puig 2007). Alterations in adipokine levels affect the development and progression of malignancies, including gastric, colorectal, biliary, pancreatic, breast, endometrial, ovarian, and kidney cancers (Buschemeyer & Freedland 2007, Majed *et al.* 2008, Wolin *et al.* 2010, De Pergola & Silvestris 2013, Gilbert & Slingerland 2013, Zhu *et al.* 2013). One of the crucial mechanisms that may explain in part the link between obesity and cancer is indeed the GH/IGF-1/insulin axis (Uehara *et al.* 2018).

Although the chronic elevation of circulating FFAs correlates with the downregulation of GH signaling (Iranmanesh & Veldhuis 1992) by acting directly on pituitary secretion (Glass *et al.* 1981, Williams *et al.* 1985), increased body mass index (BMI) correlates positively with high circulating insulin levels and insulin resistance, which could contribute to tumor incidence (De Pergola & Silvestris 2013, Liu *et al.* 2021). Obesity and prolonged hyperinsulinemia are also associated with reduced production of IGFBPs and increased levels of IGF-1 (Uehara *et al.* 2018).

In a clinical study of breast cancer, increased IGF-1 levels were associated with a 2-fold higher risk of breast cancer mortality in women with a BMI >25 kg/m^2 than in lean ones. The study also shows that a similar correlation to BMI might apply to different breast cancer types (Sparano *et al.* 2012, Duggan *et al.* 2013). A similar association between obesity and tumor development has been identified in prostate cancer, where the adipose tissue and its crosstalk with the transforming cells play a crucial role in tumor progression. This effect is partly mediated by the pro-inflammatory microenvironment

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derived from chronic hyperinsulinemia and obesity (Uehara *et al.* 2018).

Additional results were reported in a study of a mouse model of diet-induced obesity. After ~20 weeks of feeding on a high-fat diet, prostate cells showed severe insulin resistance and alterations in IGF-1 regulation. Moreover, in vitro analyses on primary cells confirmed that insulin and IGF-1 affect the pathophysiology of the prostate gland, indicating an essential role of the endocrine system in the progression of certain cancers (L-Lopez *et al.* 2017). In this context, the increase in IGF-1 exerts antiapoptotic and proliferative actions and increases the risk of prostate cancer development and progression (Roddam *et al.* 2008).

Furthermore, as reported in preclinical and clinical studies, the coexistence of several metabolic dysfunctions (such as obesity and hyperinsulinemia) and increased circulating IGF-1 correlates with the risk of developing CRC (Schoen *et al.* 1999, Giovannucci 2001, Durai *et al.* 2005, Chung *et al.* 2006, Gunter *et al.* 2008, Wolpin *et al.* 2009, Knuppel *et al.* 2020, Murphy *et al.* 2020). In a mouse model of CRC, a high-fat diet causes obesity and shows that accelerated subcutaneous tumor growth in obese female mice is associated with an increased adiposity, adipose inflammation, and IGF-1 release in the subcutaneous microenvironment. Since female hormones seem to protect from the development of this type of cancer, female mice that underwent an ovariectomy showed results superimposable to those reported for males (Bader *et al.* 2020).

Conclusions

Downregulation of GH signaling, its downstream effector IGF-1, insulin, and nutrient signaling proteins, such as PI3K, PKA, and mTOR has been linked to longevity, both in humans and in simple models, indicating a key role for nutrient-sensing pathways in longevity and incidence of chronic diseases (Fontana *et al.* 2010, Barzilai *et al.* 2012).

Nutritional status and GH/IGF-1/insulin signaling are profoundly connected, and their levels influence the incidence and progression of many cancers. Although GH and IGF-1 are not direct cancer inducers, they are known to accelerate aging and, therefore, DNA damage, but also to prevent apoptosis (Guevara-Aguirre *et al.* 2011), a combination that could explain their role in many cancers. The fact that acromegaly patients followed up for long periods show a shift from respiratory and cardiovascular disease to cancer as the major cause of death (Arosio *et al.* 2012, Mercado *et al.* 2014), together with the very low cancer rate reported for GHRD/Laron mice and humans affected by Laron syndrome, strongly indicates that the GH/IGF-1/insulin axis plays a central role in the development of many cancers. The connection between nutritional status, GH/IGF-1/insulin signaling, and cancer is evident based on CR and fasting interventions in rodent models leading to reduced cancer incidence but also in protein-restricted humans with a lower risk of cancer mortality and obese patients with higher insulin and IGF-1 showing higher cancer incidence. Animal proteins, sugar, and dairy foods rich in casein and saturated fats, pillars of the Western Diet, with their hyperglycemic and insulinotropic properties, increase IGF-1 and insulin and their signaling and appear to be at the center of a range of malignancies (Melnik *et al.* 2011). Despite such knowledge, cancer patients are still encouraged to maintain a high caloric intake and favor a high-protein diet (Arends *et al.* 2017) pointing to the need to focus both on the patient's frailty and the progression of the cancer in a coordinated way.

Since IGF-1 and insulin are strongly affected by GH, dietary interventions aimed at weight control and maintaining IGF-1 and insulin levels within a specific range represent promising strategies to sustain health and prevent frailty. Notably, in the elderly, severe dietary restrictions and very low levels of insulin and IGF-1 may not be as beneficial and could also negatively affect survival, as observed in protein-restricted elderly subjects (Levine *et al.* 2014). In conclusion, data from both nutrition/dietary restriction studies and genetic studies in both human and animal models provide strong evidence for the link between certain nutrients, the GH/IGF-1/insulin axis, and cancer. The effort to take advantage of this knowledge to prevent and treat cancer while also acting on the aging process should undoubtedly increase.

Declaration of Interest

V.D.L. has an equity interest in L-Nutra, a company that develops and sells medical food. V.D.L. has filed patents related to the FMD at the University of Southern California (USC). The University of Southern California has licensed intellectual property to L-Nutra. As part of this license agreement, the University has the potential to receive royalty payments from L-Nutra.

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Author contribution statement

M.F. and V.D.L. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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