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Weight control and cancer preventive mechanisms: role of IGF-1-mediated signaling pathways

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Abbreviations used: DCR: dietary calorie restriction**;** IGF-1: Insulin-like growth factor-1**;** DMBA: 7,12-Dimethylbenz(a)anthracene**;** ACS: American Cancer Society; VEGF: vascular endothelial growth factor; FGF: fibroblast growth factor; JNK: Jun N-terminal Kinases; TPA: 2-O-tetradecanoylphorbol-13-acetate; LID: Liver IGF-1-deficient.

Abstract

Overweight and obese not only increase the risk of cardiovascular disease and type-2 diabetes mellitus, but are also now known risk factors for a variety of cancers . Weight control, via dietary calorie restriction (DCR) and/or exercise, has been demonstrated to be beneficial for cancer prevention in various experimental models, but the underlying mechanisms are still not well defined. Recent studies conducted in a mouse skin carcinogenesis model show that weight loss induced a significant reduction of the circulating levels of IGF-1 and other hormones, including insulin and leptin, resulting in reduced IGF-1-dependent signaling pathways, i.e., Ras-MAP-proliferation and Akt-PI3K-antiapoptosis. Selective targeting IGF-1 to Akt/mTOR and AMPK pathways, via negative energy balance, might inactivate cell cycle progression and ultimately suppress tumor development. This review highlights the current studies focused on the major role of reducing IGF-1-activated signaling via weight control as a potential cancer preventive mechanism.

Keywords: *weight control, dietary calorie restriction, exercise, cancer prevention, IGF-1 signaling*

Short Title: IGF-1 Pathways and Cancer Prevention

Introduction

Maintaining a healthy body weight emerges as a strategy to generally reduce cancers and has also been suggested to reduce cancer risk. With the increasing prevalence of

obesity in both adults and children, it is important to identify the mechanism underlying cancer prevention via weight control. Current studies have focused on how understanding the molecular mechanisms of weight control, via dietary calorie restriction (DCR) and/or physical exercise, in both mouse model and human studies, prevent cancer. These studies will lead to future chemoprevention strategies for cancer.

Overweight/obesity as a risk factor of cancer

It is well known that obesity has a substantial influence on the development of many chronic diseases, including cancer. Numerous prospective and case-control studies that address the effect of body weight on cancer risk, estimate that excess body weight and sedentary life style account for about 39% of endometrial, 25% of kidney, 11% of colon, 9% of postmenopausal breast cancer, and 5% of total cancer incidence.[1] The prevalence of obesity in the U.S. rose to approximately 25% and is projected to increase to more than 40% by 2030. In children and adolescents between the ages of 6 and 17 years, the prevalence of obesity appears to be increasing even more rapidly than in adults in industrialized and developing countries.[2] It has been suggested that those who are 25% over normal weight have a 33% greater cancer risk than those who maintain an ideal body weight.[3] Therefore, weight control to prevent obesity has been recommended as a strategy for reducing cancer risk by the American Cancer Society (ACS) as early as 1996.

In obese patients and animals, insulin/leptin resistance, inflammation, and changes in hormone and growth factor concentrations are found to be key pathogenic factors that lead to many types of cancer, including breast, colon, pancreas, and

endometrium. These hormones, or growth factors, include insulin, leptin, and Insulin growth factor-1(IGF-1). They directly or indirectly provide a mitogenic effect in many cell types, especially in pre-neoplastic cells, by inducing proliferative and anti-apoptotic mechanisms.[4-6] *In vitro* studies demonstrate that insulin, through binding to the insulin receptor, increases neoplastic proliferation at both physiological and pharmacological doses.[7-9] Recently, hyperinsulinemia associated with the IGF-1 signaling pathway has been widely studied, and the condition strongly stimulates the development and growth of several tumors, especially in breast cancer.[10-12] Hyperinsulinemia is associated with increased circulating free sex hormones, such as estrogen and androgen, via inhibiting the hepatic production of sex hormone-binding globulin.[13] Altered adipokine production is also associated with insulin resistance. Adiponectin, one of the most abundant adipokines, is shown to be both anti-angiogenic and anti-inflammatory, and is lower in circulation in both obese and cancer patients.[14-18]

A high level of serum leptin in obese patients has been associated with increased cellular proliferation and angiogenesis across a wide variety of cancer subtypes, including colon, prostate and breast cancer.[19-25] The role of leptin in vascular remodeling may be independent of or coupled with vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).[26] Additionally, leptin stimulates several types of pre-neoplastic and neoplastic cells by mediating IGF-1R, resulting proliferation[27-29] and/or anti-apoptosis.[30-32]

Levels of proinflammatory cytokines, including IL-6, TNF-α and IL-1β, are found to be higher in obese mice and humans. Adipose tissue is a major source for these cytokines, contributing up to 35% of circulating IL-6.[33] Levels of these cytokines are also

elevated in cancer patients.[34,35] Although it is still unclear how these cytokines play a combined role in tumorigenesis, activation of NF-κB and STAT3 seem to be likely associated.[36-41]

Weight control via DCR inhibits tumor development in rodents

DCR is the most efficient method of weight control. The first work to show that incidence of tumors in mice positively correlated with food intake was published in 1944 by Tui and colleagues.[42] To date, DCR has been the most widely studied and most potent, broadly acting dietary intervention for cancer prevention in various experimental models.[43,44] DCR is a dietary regimen that restricts calorie intake without malnutrition (usually by 20%–40% relative to *ad libitum*-fed controls from lipids and carbohydrates, but same amount of proteins, micronutrients and minerals, etc.). DCR-fed *wildtype* animals are typically healthier, live longer, and more active than their *ad libitum*-fed counterparts[45].

DCR inhibits various spontaneous tumor developments in experimental animals. In rodents, a 20-40% below the usual ad libitum intake initiated early in life led to approximately 20-60% reduction in tumor incidence, including tumors of mammary, liver, colon, skin, pancreas, bladder, and leukemia.[46,47] In p53-deficient mice, both juvenile- and adult-initiated calorie restriction to 60% of *ad libitum* intake, significantly delayed tumor development.[48,49] In Apc^{Min} mice, calorie intake restricted by 40% of the *ad libitum*-fed mice reduced intestinal polyps by 57%.[49,50] DCR is also well documented to suppress carcinogen-induced carcinogenesis, like benzo(α)pyrene[51] and 7,12-dimethylbenz(α)anthracene (DMBA)[52].

Weight control via exercise

Epidemiological studies report that physical activity can reduce the risk of many types of cancers, especially cancer of the prostate, breast, endometrial, and lung.[53] Evidence suggests that 4–7 hours per week of moderate to vigorous physical activity is required for adequate risk reduction.[53] However, in the U.S., adults are not achieving the recommended amounts of physical activity, according to ACS guidelines.[54-59]

Despite the large numbers of studies conducted, cancer prevention by physical activity in animal models is not consistent. This is largely due to the lack of precise quantitative characteristics of duration and intensity of exercise as well as the control of the dietary calorie intake. Therefore, the impact of exercise on cancer development should be considered in combination with an isocaloric diet.

Decreased IGF-1 signaling in cancer prevention

There are several hypotheses describing mechanisms by which weight control via DCR and/or exercise may reduce tumor development. Some hypotheses include decreased oncogene expression, improved DNA repair, enhanced scavenging of reactive oxygen species, and altered levels of cancer-related hormones.[60]

Hormone alteration seems to be a critical factor for cancer prevention by weight control, due to the significant role of hormones in regulating cellular growth. Previous researchers have found that the levels of IGF-1[62-64], insulin[61], and leptin[61,65-67] decreased significantly in rodents in response to DCR.

IGF-1 is a major endocrine and paracrine regulator of cellular growth and metabolism. Binding of IGF-1 to IGF-1R activates many signaling pathways, including Jun N-terminal Kinases (JNK), p38 MAPK and PI3K via activation of receptor tyrosine kinases and/or the Ras proto-oncogene, to mediate suppression of apoptosis and contribute proliferation and cell growth.[74-78] IGF-1R is overexpressed in many tumors.[70,71] Abundant epidemiologic evidence supports the hypothesis that IGF-1 is involved in several types of human cancers.[68,69] Adult HK1.IGF-1 mice that overexpressed IGF-1 spontaneously developed papillomas faster than non-transgenic littermates.[72,73] Adult HK1.IGF-1 mice showed enhanced signaling through the Akt/mTOR pathways[79], which suggested a critical role of IGF-1 in activating Akt/mTOR pathway that regulates cell proliferation, survival and energy metabolism. Activated mTOR signaling through the Akt/mTOR pathway in Akt overexpressing mouse caused alterations in epidermal proliferation and differentiation.[79] The mice are more sensitive to topical 12-O-tetradecanoylphorbol-13-acetate (TPA) treatment. Activation of IGF-1R also indirectly acts with other cancer-related molecules, such as p53, known to arrest cell growth and induce apoptosis with increased levels of p21 and reduced Bcl-2.[80]

Reduction in glucose and insulin levels, as well as IGF-1, has been well documented in DCR-fed mice from different labs. Levels of circulating IGF-1 are influenced by dietary energy intake, which may be due to changing growth hormone-regulated hepatic synthesis of IGF-1.[81] Restoration of IGF-1 in p53-deficient mice reversed DCR-induced cancer protection, suggesting a requirement of reduced levels of IGF-I.[16] While 20% DCR-fed SENCAR mice showed a significant reduction of plasma IGF-1 levels, a remarkable decrease of IGF-1-dependent Ras/MAPK and PI3K/Akt

signaling was demonstrated in TPA-stimulated skin tissues.[82,83] Both down-expression of PCNA as a biomarker of proliferation and up-expression of Caspase-3 as a biomarker of apoptosis were also subsequently found in those mice.[82,83]

Diet-induced changes in Akt/mTOR signaling have been reported in various organ tissues (i.e., liver, skin epidermis, and mammary fat pad). DCR-induced increase of AMP/ATP ratio may inhibit AMPK signaling that regulates mTOR activity and thereby inhibits the targeted protein production. These changes appear to be related to the reduction of circulating IGF-1 levels. In such study, 30% DCR regimen for 15-17 weeks is sufficient to lower circulating IGF-1 concentrations and inactivate Akt and mTOR signaling in multiple epithelial tissues, regardless of genetic background of the experimental mice.[84] These results suggest that DCR induced a decrease of IGF-1 should play a central role in response with negative energy balance-altered depression of mTOR activity.[85]

In addition, an important study has revealed that DCR contributes to mammalian cell survival by inducing Sirtuin 1 (SIRT1) deacetylase, which deacetylates the DNA repair factor Ku70. Ku70 can prevent the proapoptotic factor Bax from mitochondrial entry, therefore inhibiting stress induced apoptosis.[86] This impact is probably mediated by insulin/IGF-1 because treatment with insulin and/or IGF-1 can reduce SIRT1 deacetylase expression.[86]

In humans, 15 weeks of moderate exercise changes the levels of fasting insulin, glucose, IGF-I, IGF-II, IGFBP-1, IGFBP-3, and IGF-I:IGFBP-3 molar ratio.[87,88] However, a 12-month exercise regimen did not change IGF-1 and IGFBG-3 levels in

postmenopausal women.[89] Regular exercise alters the serum IGF-1 axis *in vivo* and reduces prostate (LNCaP) tumor cell proliferation by enhancing the function of the p53 gene [90,91] In SENCAR mice, weight loss by 10-week physical activity with iso-caloric intake as sedentary controls was able to inhibit PI3K signaling and increase caspase-3 activity. [82] These effects were partially reversed by IGF-1 restoration.[82] Microarray analysis comparing TPA-induced gene expression profiles in DCR- or exercise-treated mouse skin tissues revealed 411 genes affected by DCR versus only 67 affected by exercise with iso-caloric intake, including PI3K and MAPK pathway genes.[82-83] Similar results of mammary gland gene expression are found in C57BL/6 mice with a 30% DCR versus exercise.[92] The increased expression of fatty acid elongase-1 in treadmill exercised mice with iso-caloric intake suggests that exercise may affect the phospholipid profile.[93] In addition, a lipidomics study using electrospray ionization-tandem mass spectrometry demonstrated that 57 phospholipids were significantly changed among a total of 338 species detected, and 25 species were closely related to exercise by a stepwise discriminant analysis.[93-94] These combined results indicate that DCR and/or exercise may target IGF-1-dependent signaling directly for a potential cancer prevention.

IGF-1 signaling as a potential target for cancer prevention

Effective prevention and treatment strategies are urgently needed for anti-tumorigenesis. Considering the central role that IGF-1 played on cancer development, decreasing IGF-1 signaling either by chemical intervention or genetic interference has been intensively studied. Liver IGF-1-deficient (LID) mice have been utilized to mimic the effect of DCR on reducing circulating IGF-1.[95] These mice had about 75% reduction in the level of

circulating IGF-1. Repressed IGF-1R, EGFR and Akt/mTOR were observed in the skin tissue of LID mice after TPA treatment. LID mice initiated with DMBA and promoted with TPA, developed fewer and slower growing of papillomas compared with untreated littermates.[95] In another study that tested if DCR effect can be replicated by chemotherapy, mice transplanted with Panc02 murine pancreatic cancer cell were treated with either DCR or rapamycin for 20 weeks.[96] Rapamycin treatment (2.5 mg/kg intraperitoneal every other day) did not decrease body weight, IGF-1 or leptin level, unlike DCR, but inhibited glucose responsiveness. Mice that received rapamycin had depressed mTOR signaling and had significantly reduced tumor volume compared to untreated mice, although to a lesser extent than DCR-fed mice. These results suggest that the downstream modulators of IGF-1 pathway can be a potential target for cancer prevention supplements.

Conclusion

Many epidemiological, clinical, and experimental studies have revealed a positive relationship between weight control via DCR or physical activity, and the frequency of various cancers. Reductions in the levels of circulating IGF-1 and other mitogenic hormones/growth factors, including insulin and leptin induced by DCR or physical activity, efficiently inactivate the downstream signaling pathways via IGF-1R as summarized in details in Figure 1. Future studies aimed at further elucidating the mechanisms underlying the cancer prevention possibilities of weight control may finally lead to efficient pharmacologic approaches that can be used alone or combined with weight control.

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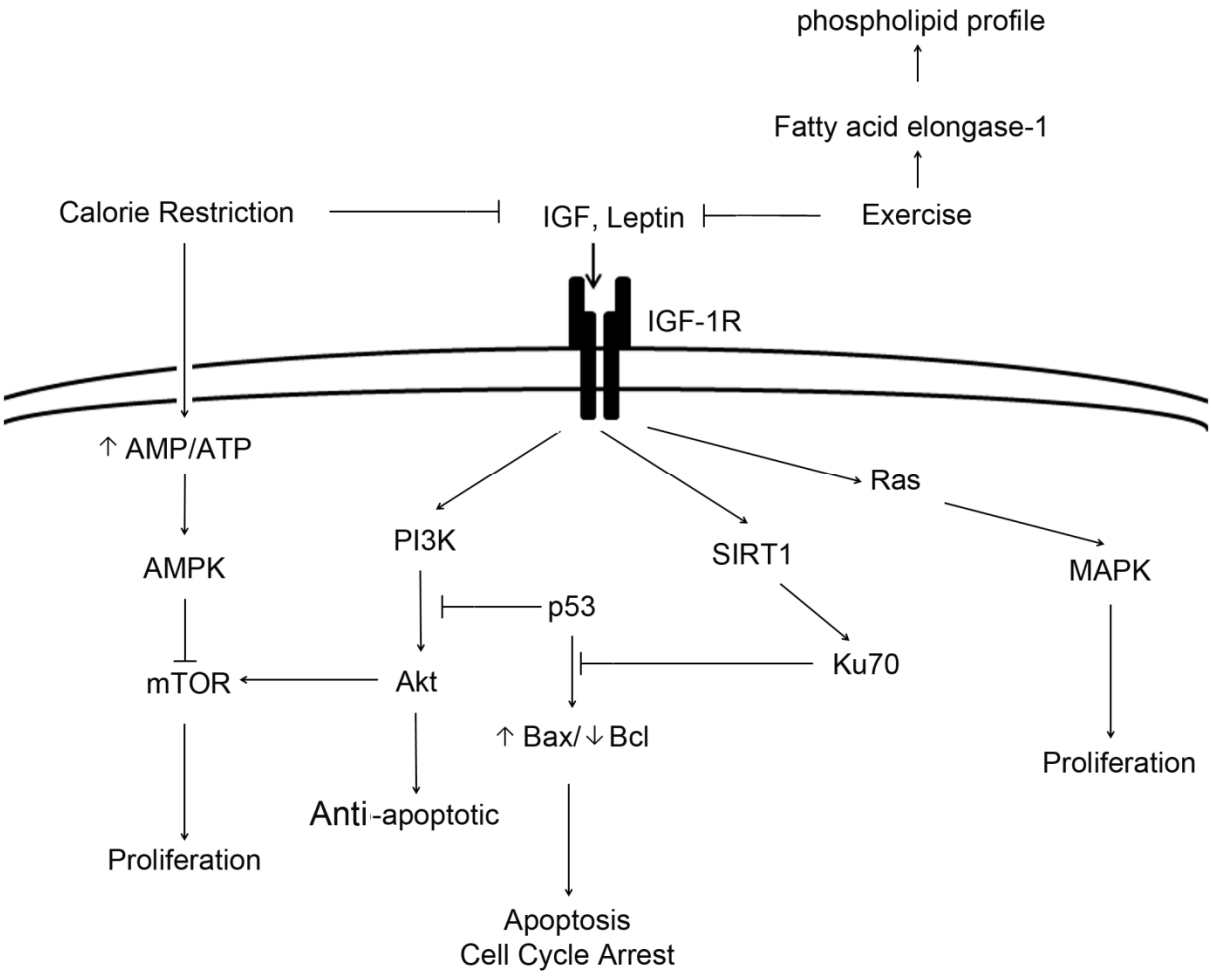
Figure legend:

Figure 1. Schematic illustration of IGF-1- and/or leptin-induced signaling pathways that may be targeted by weight control via dietary calorie restriction and exercise.


phospholipid profile
Fatty acid elongase-1
Calorie Restriction
IGF, Leptin
Exercise
IGF-1R
↑ AMP/ATP
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PI3K
SIRT1
AMPK
MAPK
p53
mTOR
Akt
Ku70
↑ Bax/↓ Bcl
Proliferation
Anti-apoptotic
Proliferation
Apoptosis
Cell Cycle Arrest

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