Weight control, endocrine hormones and cancer prevention

Brenee King, Yu Jiang, Xiaoyu Su, Jianteng Xu, Linglin Xie, Joseph Standard and Weiqun Wang

Department of Human Nutrition, Kansas State University, Manhattan, KS, 66506, USA
Correponding author: Weiqun Wang. Email: wwang@ksu.edu

Abstract

The prevalence of obesity is increasing which becomes worrisome due to its association with several diseases and certain types of cancers. While weight control through dietary caloric restriction and/or physical activity protects against cancer in animal models, the underlying mechanisms are not fully defined. Weight loss due to negative energy balance is associated with alterations of multiple growth factors and endocrine hormones. The altered hormones and hormone-related functions appear to be responsible for anti-cancer mechanisms. In this review, we summarize the recent studies related to weight loss and the altered endocrine hormones, focusing on the reduced levels of the mitogenic insulin-like growth factor 1 (IGF-1) and adipokine leptin as well as the raised levels of adiponectin and glucocorticoids. The potential molecular targets of these hormone-dependent signalling pathways are also discussed. Considering the increasing trends of obesity throughout the world, a better understanding of the underlying mechanisms between body weight, endocrine hormones and cancer risk may lead to novel approaches to cancer prevention and treatment.

Keywords: Weight control, dietary calorie restriction, physical activity, IGF-1, leptin, glucocorticoids, cancer prevention

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Introduction

The obesity rate has grown rapidly in the past decades.[1] Its prevalence is shown by nearly two-thirds of adults in the United States (US) now being overweight or obese. Obesity is associated with increased risk for several chronic diseases, including various types of cancers.[2] A prospectively studied cohort of adults in the US including over 900,000 subjects demonstrated that increased body weight was associated with increased death rates for cancer.[3] The high prevalence of being overweight or obese is supported by a lifestyle involving over-consumption of energy, combined with low physical activity.[4] The International Agency for Research in Cancer within the World Health Organization states that limiting one's weight gain during adulthood or increasing one's physical activity reduces the risk for a number of cancers. Consequently, there is evidence that weight control via dietary calorie restriction (DCR) and/or exercise reduces cancer risk in experimental animal studies.

DCR refers to a decrease of energy intake from fats and carbohydrates, while maintaining the same levels of proteins and essential micronutrients. Since an initial animal study performed in 1909 by Moreschi,[5] scientists have recognized DCR as an effective dietary means for cancer prevention. Both chemically induced and spontaneously arising cancers are suppressed by DCR, including cancers such as mammary, liver, colon, skin, pancreas and leukemia. DCR has been tested in a wide range of animal models from flies to rodents. Furthermore, a relationship between reduced DCR and decreased tumour rates has been established in rodents.[6]

Increasing energy expenditure via exercise has also been found to be effective for weight loss and cancer prevention.[7] A large cohort study including over 42,000 postmenopausal women in the US found that physical activity of light and moderate intensity was associated with a reduced risk of endometrial cancer.[8] Additionally, a large cohort study including 79,771 Japanese men and women found that increased daily physical activity decreased cancer risk.[9] A review of epidemiological studies by Friedenreich and Orensterin stated that cancer prevention by physical activity was convincing for colon and breast cancer, probable for prostate cancer and possible for endometrium and lung cancer, while some other types of cancers seemed less sufficient and conclusive.[10] It was found that physical activity, both by forced treadmill and voluntary wheel, was effective in reducing the incidence and multiplicity of azoxymethane-induced colon carcinomas in F344 rats.[11] Exercise also protects against lung,[12] mammary[13] and leukemia metatasis.[14] However, exercise-induced cancer inhibition appears less consistent and/or less potent than calorie restriction. By using treadmill exercise, our laboratory

found the effects of exercise on body weight control and anti-tumorigenesis were mixed if physical activity was not accompanied with iso-caloric intake.[15] Research reported by Moore *et al*.[16] suggested that negative energy balance, not exercise alone, inhibited the development of intestinal polyps in APC^{Min} mice. Overall, the impact of physical activity on cancer prevention is positive, but not as reliable when compared to the DCR approach.

Biochemical or molecular mechanisms underlying the complex relationship between weight control and cancer prevention are not well known. Recently, the National Cancer Institute's Provocative Questions called for research proposals in this research area (RFA-CA-12-015 and RFA-CA-12-016). Two of the six provocative questions in 2012–2013 were how obesity contributes to cancer risk and how the level, type or duration of physical activity influences cancer risk and prognosis. It is well documented that body weight change corresponds to multiple changes in plasma levels of growth factors or hormones. For instance, circulating hormone levels are dramatically changed during DCR-fed weight loss, including reduced IGF-1 and leptin,[15] but increased adiponectin[17] and glucocorticosteroids.[18] Generally speaking, these hormones are critical in the maintenance of cellular growth, proliferation and apoptotic functions. Alterations to these hormone levels and hormone-related metabolic functions may be responsible for anti-carcinogenic mechanisms.[2,19]

IGF-1: a key mitogenic factor for cellular proliferation and inhibition of apoptosis

Insulin-like growth factor-1 (IGF-1) is a 70-amino acid polypeptide that has a high sequence similarity to insulin. IGF-1 plays an important role in cell growth and survival. IGF-1 is made in most tissue types, but the majority of plasma IGF-1 is biosynthesized in the liver.[20] IGF-1 binding proteins (IGF-BPs), in which there are six homologs, are responsible for modulating the circulating levels of IGF-1 and its bioavailability. IGF-BP3 is the most abundant IGF-1 binding protein in humans.[21] Free IGF-1 or IGF-1 bound to IGF-BPs can cross the capillary endothelium and reach target tissues. IGF-BPs are degraded by proteases in tissues as well as in the circulation, through which IGF-1 is freed and able to interact with IGF-1 receptors (IGF-1R).[22] IGF-1R is a member of the receptor tyrosine kinase super family whose structure, particularly in the tyrosine kinase domain, is similar to that of the insulin receptor. Binding of IGF-1 to its receptor results in autophosphorylation and activation of downstream mitogenic signalling networks, such as phosphatidylinositol-3-kinase (PI3K)-Akt and Ras-mitogen activated protein kinase (MAPK) pathways.[23] It is well known that PI3K-Akt and Ras-MAPK cascades correspond to anti-apoptotic and proliferative pathways, respectively.

A multiethnic cohort study has shown that an increase in circulating concentrations of IGF-1 and low levels of IGF-BP3 result in a high risk for colorectal cancer,[24] while a case–control study reported a similar association for bladder cancer.[25] Men in the highest quartile of plasma IGF-1 had a 4.3-fold higher risk of prostate cancer when compared to men in the lowest quartile.[26] With regard to breast cancer, IGF-1R activation can enhance transformation, stimulate proliferation and promote metastasis.[27] Data obtained from various ovarian cancer cell lines have linked IGF-1R mRNA expression to tumour stage and drug resistance.[28] The IGF system has been implicated in almost all phases of lung oncogenesis[29] and a correlation between the circulating IGF-1 levels and cancer risk was also found in colon cancer.[30]

In order to detect a potential role of IGF-1 signalling in multistage mouse skin carcinogenesis, the DiGiovanni laboratory developed a transgenic mouse model (HK1.IGF-1) in which IGF-1 was overexpressed in the epidermis by the human keratin 1 promoter.[31] The authors found that when compared to wild type mice, HK1.IGF-1 transgenic mice were more sensitive to tumour promoters such as TPA after initiation with DMBA. The transgenic mice developed tumours more rapidly and there was an increased number of tumours per mouse.[31,32] Additionally, squamous papillomas and carcinomas developed spontaneously in a similar transgenic mouse model BK5.IGF-1, which overexpressed IGF-1 in the basal layer of skin epidermis.[32] Mechanistically, the PI3K-Akt pathway is important in IGF-1-mediated skin promotion. In DMBA initiated IGF-1 transgenic mice, inhibition of PI3K activity significantly blocked epidermal proliferation as well as skin tumour development.[33] Overall, these studies support the notion that increased levels of circulating IGF-1 may be causal in the development of multiple cancers.[34]

Given that high IGF-1 levels are associated with cancer development, attempting to lower IGF-1 levels could be beneficial in decreasing cancer incidence. Thus, manipulations of plasma IGF-1 levels have been applied in cancer prevention strategies. Weight control is known to alter hormone levels; more specifically, it can reduce the levels of IGF-1. Ruggeri *et al*.[35] initially reported that DCR significantly decreased serum IGF-1 in female Sprague-Dawley rats at the first and third weeks following the start of the experiment. Studies from our laboratory showed that IGF-1 was significantly decreased by dietary calorie restriction and restoration of IGF-1 significantly abolished PI3K reduction in treadmill-exercised mice whose feeding was comparable to their sedentary controls.[15,36] We recently reviewed the potential IGF-1-mediated signalling targets by weight control-induced cancer prevention.[37] To elucidate a causal-link mechanism by which the reduction of IGF-1 is required for anti-tumorigenesis, we restored IGF-1 in DCR-fed mice. However, the DCR-induced anti-tumorigenesis was not significantly reversed (Figure 1A). Overall, the above results show that the reduction of IGF-1 levels and subsequent down-regulation of IGF-1 signalling pathways, as a consequence of dietary restriction may, in part, contribute to anti-tumorigenic activity.

The impact of physical activity on IGF-1 reduction and cancer prevention is complicated mainly due to inconsistencies in parameters such as, exercise protocols, timing of IGF-1 measurements and heterogeneity of subjects. Long-term exercise decreased plasma IGF-1 levels in endurance runners when compared to sedentary individuals, but were not decreased in short bout exercise or physical traning.[38]

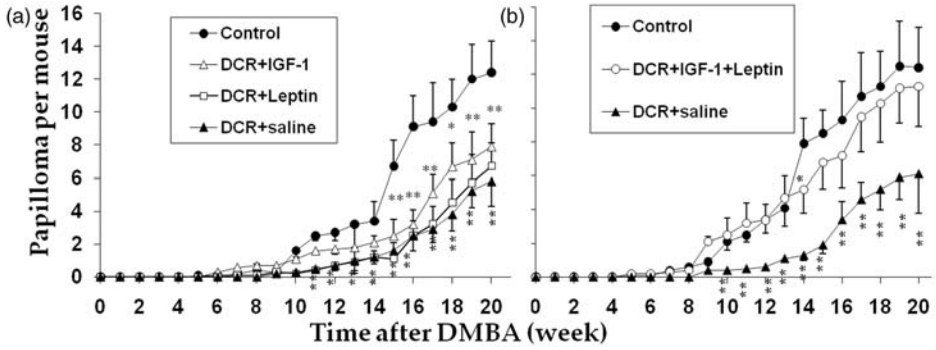

Figure 1 Effects of restoration of individual or combined IGF-1 and leptin on DCR-induced anti-tumorigenic activity. According to a published method with minor modification,[18] a two-stage skin tumorigenesis model in SENCAR mice was initiated by 10 nmol DMBA (7,12-dimethyl-benz[α]anthracene) and promoted by 3.2 nmol TPA (12 -*O*-tetradecanoylphorbol-13-acetate) biweekly for 10 weeks. Mice were fed 20% DCR-diet one week after DMBA. Individual IGF-1 at 5 μg/μl or leptin at 0.5 μg/μl (A) or the combination of IGF-1 and leptin (B) were implanted by osmotic minipumps (Alzet Osmotic Pumps, Cupertino, CA). The visible skin tumours were inspected and counted weekly. Data are presented by Mean ± SE, $^{*}P < 0.05$, $^{**}P < 0.01$ vs. the controls, $n = 12$–15 per group

Animal data obtained from our laboratory showed exercise alone with *ad libitum* feeding was not adequate to decrease plasma IGF-1 levels, but exercised mice that were pair fed with their sedentary counterparts had modestly reduced IGF-1 levels.[15] Our evidence along with others[39] suggest that a fundamental requirement for IGF-1 reduction and involvement in cancer prevention involves a negative energy balance.

Leptin: a link between adipokines and cancer risk

Adipokines such as leptin and adiponectin are secreted by adipose tissues, which provide metabolic and endocrine functions. Plasma levels of leptin correlate closely with body mass index as well as total amount of body fat.[40,41] Leptin regulates appetite and controls body weight through signalling to the hypothalamus which suppresses food intake and stimulates energy expenditure.[42] While leptin is mainly secreted by adipocytes, other organ cells such as the placenta, ovaries, skeletal muscle, pituitary gland, stomach and liver can produce small amounts of leptin under certain circumstances.[43] Due to the ubiquitous nature of its receptor, leptin plays a role in a diverse range of physiological functions both in the central nervous system and within peripheral tissues.[42,44,45] Activation of the leptin receptor stimulates IGF-1-like signalling such as Ras-MAPK and PI3K-Akt. Additional signalling cascades induced by leptin include PKC-p38 kinase, and transcriptional factor AP-1 component proteins such as c-fos, c-jun and junB.[46,47]

Leptin is involved in the pathogenesis of cancer by stimulating growth, migration and invasion in *in vitro* cellular models. Leptin can induce cell proliferation in breast cancer cell lines though activation of MAPK and PI3K.[48] Additionally, leptin can stimulate estrogen synthesis via increased aromatase gene transcription and protein activity, suggesting it might be responsible for the resistance to anti-estrogens during hormonal treatment of breast cancer.[49] In HT29 colon cancer cells, leptin induced cell growth and blocked apoptosis through stimulation of the extracellular-signal-regulated kinase (ERK)1/2 and NFκB pathway.[50,51] Moreover, the mitogenic activity of leptin has also been demonstrated in prostate, pancreatic, ovarian and lung cancer cells.[52,53] To elucidate a potential causal-link mechanism by which the reduction of leptin may account for anti-tumorigenic activity, we also restored leptin in DCR-fed mice. The results are similar to IGF-1 restoration (Figure 1A), i.e. no significant difference was found between DCR/leptin implantation and DCR/saline groups. It is interesting, however, that the inhibition of tumorigenesis in the epidermis of DCR-fed mice is fully abrogated by implanting both IGF-1 and leptin (Figure 1B), constituting direct evidence that leptin may act as a co-promoter for mitogenic effects of IGF-1 on tumorigenesis. Overall, these data suggest that together both leptin and IGF-1 are involved in tumour progression. As such, manipulation of plasma leptin levels may provide a potential target in cancer prevention and treatment.

Since plasma levels of leptin are positively associated with body weight and body mass index, weight control has the potential to be effective in lowering circulating leptin. Ishigaki *et al*. showed that plasma concentrations of leptin were significantly lower in endurance runners when compared to sedentary individuals.[53] Studies from our laboratory showed that plasma levels of leptin were significantly decreased in DCR-fed mice and pair-fed exercised mice in comparison to control mice.[15] While further research is needed to fully characterize the specific role of leptin in cancer development, the above evidence suggests that the reduction of leptin concentrations could contribute to the protective effects of weight control.

Additional hormones implicated in cancer prevention by weight control

In addition to IGF-1 and leptin, weight loss can also alter the levels of other hormones such as insulin, adiponectin and glucocorticoids. Insulin is important in the regulation of blood glucose levels. In the liver, it stimulates glycogen synthase and inhibits glycogen phosphorylase as a means to promote glycogen synthesis. In muscle and fat tissues,

insulin induces the uptake of glucose through increased GLUT4 expression. Binding of insulin to its receptor, the insulin receptor, activates signalling pathways through various phosphorylation cascades involving the insulin-receptor substarate-1, Akt, MAP kinase and PI3K kinase.[54] As such, insulin can induce the growth of both normal and cancerous cells. Also, insulin promotes the bioactivity of IGF-1 by either increasing the number of growth hormone receptors in the liver or reducing hepatic secretion of IGF-BP1, which binds and inhibits the activity of IGF-1.[55,56] Insulin receptor and IGF-1R are frequently overexpressed in tumours and their expression levels have been correlated with tumour aggressiveness.[57,58]

Obesity or lack of physical activity is found to be a major factor inducing insulin resistance and hyperinsulinemia. Epidemiological studies have shown that increased plasma insulin is associated with a high cancer risk.[59] However, DCR and/or regular exercise have been linked to decreased plasma insulin in some studies.[60] Further studies evaluating the association between insulin and body weight-related cancer risk seem warranted.

Another adipokine known as adiponectin is also secreted by adipose tissue and plays an important role in obesity-related disorders. It exists in several forms: trimers, hexamers, high-molecular weight multimers and globular. Adiponectin is able to exert its biological effects through binding to the specific receptors AdipoR1, AdipoR2 and T-cadherin.[61,62] The relationship of serum levels of adiponectin with cancer risk has been investigated in both epidemiological and animal model studies. Some case–control studies showed that low serum adiponectin levels were associated with an increased risk of breast cancer in women.[63,64] Adiponectin was also found to be lower in prostate cancer patients when compared to healthy controls, and its levels were negatively correlated with histological grade and disease stage.[65] Additionally, gastric and colon cancer patients were found to have lower plasma adiponectin levels which were linked to increased tumour size and higher risk, respectively.[66,67] Overall, the above mentioned studies suggest there may be an inverse relationship between plasma levels of adiponectin and cancer. Therefore, an increase of plasma adiponectin could potentially be beneficial in cancer prevention.

Weight control through DCR and/or exercise enhances plasma levels of adiponectin, but the cumulative results are not conclusive. Calorie-restricted rats had higher levels of plasma adiponectin which resulted in reduced blood glucose, plasma insulin and triglycerides when compared with *ad libitum* controls.[68] However, a human study found that serum concentrations of adiponectin did not change in individuals' exposure to high altitude following three weeks of calorie restriction.[69] With regard to exercise, Jamurtas *et al*.[70] showed that 48-hours post-acute exercise did not change plasma adiponectin levels, although adiponectin levels were significantly increased in individuals with type 2 diabetes following four weeks of physical training.[71] Perhaps adiponectin's cancer protection is more effective in overweight individuals who undergo calorie restriction, and the protective effect may be mitigated in normal weight individuals.

Furthermore, studies have been conducted to assess the functional effects of adiponectin. Studies in myelocytes showed that adiponectin suppressed growth, induced apoptosis and inhibited TNF-alpha production.[72] Adiponectin was found to inhibit cell proliferation and induce cell cycle arrest and apoptosis in MDA-MB-231 and MCF-7 breast cancer cell.[73] A review by Paz-Filho *et al*. summarizes the role of adiponectin in various cancers such as prostate, breast, colon, endometrial and others.[61] While more studies aimed at elucidating a beneficial role of adiponectin in cancer prevention by weight control seem needed, the Thompson laboratory reported that plasma levels of adiponectin were the most valuable biomarkers in predicting carcinogenic response in a rat model.[74]

Last but not the least, glucocorticoid hormones are usually increased in response to weight loss. Glucocorticoids are a class of steroid hormones. They have extensive functions including modulation of metabolism, suppression of inflammation and inhibition of glucose uptake.[75] Glucocorticoid hormones act by binding to intercellular glucocorticosteroid receptors which lead to the formation of a receptor–ligand complex.[76] This complex dissociates from heat shock proteins allowing it to translocate into the nucleus where it binds to glucocorticoid response elements and act as a transcription factor.[77] Activated glucocorticoid receptors have the potential to interfere with other transcription factors, such as AP-1 and NFκB which are crucial in the regulation of a number of genes involved in differentiation, inflammation, cell proliferation, apoptosis, oncogenesis and other biological processes.[78,79]

Glucocorticoid steroids have been shown to be elevated in DCR-fed animals[80] and hypothesized to be partially responsible for the inhibitory effects of caloric restriction with regard to experimentally induced cancers.[81,82] In an effort to confirm these results, Zhu *et al*.[83] found the incidence and multiplicity of mammary tumours were decreased in female Sprague-Dawley rats who had been administered corticosterone in their diet. Additionally, a decrease of plasma corticosterone levels via adrenalectomy surgery was found effective in abrogating the preventive effect of DCR on skin and lung tumour development in SENCAR and A/J mice, respectively.[18,84,85] While it may appear that the increase in glucocorticoid steroid levels alone may account for the inhibitory effects on cancer development, Zhu *et al*.[83,86] discuss that during DCR there is likely a simultaneous mechanism involving the metabolism of both glucocorticoid steroids and IGF-1. Overall, these data suggest increased glucocorticoid steroid levels in response to weight loss may be an additional mediator in cancer prevention through calorie restriction.

Conclusion

As we learn more about the protective mechanisms related to weight control, it becomes apparent that multiple hormones and hormone-related molecular targets are involved. The reduction of IGF-1 in response to weight loss via DCR or exercise with iso-caloric intake is required for less mitogenic promotion in proliferation and anti-apoptotic signalling pathways as illustrated in Figure 2. In addition, many

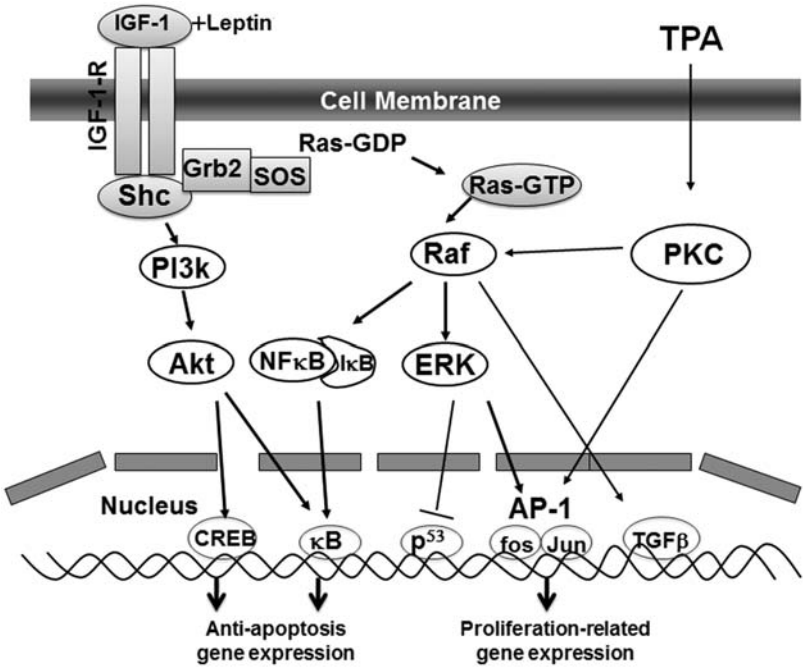

Figure 2 Schematic of IGF-1 and/or leptin verse TPA induced oncogenic signalling pathways. Signalling from the IGF-1 receptor is via Ras-Raf-ERK and PI3K-Akt pathways, leading to transcription factor AP-1-induced proliferative and CREB/κB-induced anti-apoptotic effects. In addition to the central nervous system, leptin also acts at peripheral tissue cells via the leptin receptor that may stimulate IGF-1-like signalling such as Ras-MAPK, PI3K-Akt, and transcriptional factor AP-1. Both IGF-1 and leptin may thus co-activate mitogenic Ras-MAPK-proliferation and PI3K-Akt-antiapoptosis, which appear to engage in cross-talk with TPA-induced oncogenic signalling and thus promote cancer development

other hormones may additively work together. DCR- and/or exercise-induced weight loss reduces not only body fat, but also adipocyte-released pro-inflammatory adipokines such as leptin. It seems that leptin may cumulatively act as a co-mitogenic promoter with IGF-1 in signalling cross-talk with TPA-induced oncological cascades (Figure 2). Therefore, a reduction of both IGF-1 and leptin levels during weight control may be fundamentally required for cancer prevention. Considering the increasing trends of obesity throughout the world, a better understanding of the complex interactions among body weight, endocrine hormones, and cancer risk may lead to novel approaches to cancer prevention and treatment.

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