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EDITORIAL

Interplay of adipokines and myokines in cancer pathophysiology: Emerging therapeutic implications

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Abstract

Excess body weight constitutes a worldwide health problem with epidemic proportions impacting on the risk and prognosis of several disease states including malignancies. It is believed that the metabolic changes associated with weight gain, particularly visceral obesity, and physical inactivity could lead to dysfunctional adipose and muscle tissues causing insulin resistance, low-grade chronic inflammation and abnormal secretion of adipokines and myokines. The complex paracrine and endocrine interconnection between adipokines and myokines reflects a yin-yang balance with important implications in processes such as lipolysis control, insulin sensitivity and prevention from obesity-driven chronic low-grade inflammation and cancer promotion through anti-inflammatory adipokines and myokines. Furthermore, the complex pathophysiology of cancer cachexia is based on the interplay between muscle and adipose tissue mediated by free fatty acids, various adipokines and myokines. The purpose of this editorial is to explore the role of the adipose and muscle tissue interplay in carcinogenesis, cancer progression and cachexia, and to examine the mechanisms underpinning their association with malignancy. Understanding of the mechanisms connecting the interplay of adipokines and myokines with cancer pathophysiology is expected to be of importance in the development of therapeutic strategies against cancer cachexia. Advances in the field of translational investigation may lead to tangible benefits to obese and inactive persons who are at increased risk of cancer as well as to cancer patients with cachexia.

Key words: Adipokine; Myokine; Cancer; Cachexia; Interleukin-15; Interleukin-6; Obesity; Myostatin

Core tip: The complex paracrine and endocrine interconnection between adipokines and myokines reflects a yin-yang balance with important implications in processes such as lipolysis control, insulin sensitivity and prevention from obesity-driven chronic low-grade inflammation and cancer promotion through anti-inflammatory adipokines and myokines. In addition, the complex pathophysiology of cancer cachexia is based on the interplay between muscle and adipose tissue mediated by free fatty acids, various adipokines and myokines. Advances in the field of translational investigation may lead to tangible benefits to obese and inactive persons who are at increased risk of cancer as well as to cancer patients with cachexia.

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INTRODUCTION

Excess body weight constitutes a worldwide health prob-

lem with epidemic proportions impacting on the risk and prognosis of several disease states including cardiovascular disease (CVD), type 2 diabetes mellitus (t2DM) and common forms of cancer, such as colon cancer, postmenopausal breast cancer, endometrial cancer, renal cell cancer and esophageal adenocarcinoma[1-10]. Globally, about 25% of cancer cases are due to overweight/obesity and sedentary lifestyle[11].

Obesity prevents muscle gain and the combination of obesity and loss of muscle mass could lead to elevated health risks including obesity-associated malignancies. It is believed that the metabolic changes associated with weight gain, particularly visceral obesity, and physical inactivity could lead to dysfunctional adipose and muscle tissues causing insulin resistance, low-grade chronic inflammation and abnormal secretion of adipokines and myokines[6,12,13]. Therefore, the adipose-muscle cross-talk plays a critical role in cancer promotion. On the other hand, in the context of cancer cachexia which characterizes cancer patients with advanced stage, the interplay between adipose tissue and skeletal muscle that occurs through adipokines and myokines is an exciting field of research with emerging novel therapeutic implications[14-16].

The purpose of this editorial is to explore the role of the adipose and muscle tissue interplay in carcinogenesis, cancer progression and cachexia, and to examine the mechanisms underpinning their association with malignancy. Understanding of the mechanisms connecting the interplay of adipokines and myokines with cancer pathophysiology is expected to be of importance in the development of preventive and therapeutic strategies against cancer.

INTERPLAY OF ADIPOKINES AND MYOKINES IN CANCER ETIOPATHOGENESIS

Adipose tissue, main adipokines and cancer

In addition to its inert lipid-storing capacity, adipose tissue represents the largest endocrine organ modulating energy homeostasis, metabolism, inflammation, immunity and endocrine balance[6]. Adipose tissue synthesizes and secretes more than fifty hormones and cytokines, known as adipokines[6]. As adipose tissue expands in obesity, the amount of anti-inflammatory adipokines, particularly adiponectin, decreases and the amount of pro-inflammatory adipokines with an oncogenic potential, such as leptin, resistin, visfatin and chemerin, and cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1 and IL-6 increases[6,17]. Obesity-driven chronic low-grade inflammation is also involved in insulin resistance (IR), which is characterized by hyperinsulinemia, increased levels of growth factors such as insulin-like growth factor-I (IGF-I) and activation of transcriptions factors participating in pro-inflammatory response and cell-cycle regulation, like nuclear factor kappa-B (NF-κB), which can promote carcinogenesis[6,17,18]. Important cancer-related adipokine effects are summarized below.

Adiponectin is a 30-kDa, 244-amino-acid adipokine exerting insulin-sensitizing, anti-inflammatory and anti-neoplastic effects[6]. The majority of epidemiologic evidence has connected *in vivo* hypoadiponectinemia with an increased risk for IR, metabolic syndrome (Mets), t2DM, CVD and obesity-associated malignancies[6,19] as well as with a more aggressive cancer phenotype characterized by higher histologic grade, large size of tumor, lymph node invasion, distal metastases or estrogen receptor negativity for breast cancer[6,20-25]. In summary, adiponectin presents anti-tumorigenic effects *via* two mechanisms: (1) it can act directly on cancer cells by modulating receptor-mediated signaling pathways, including mitogen-activated protein kinase (MAPK), AMP-activated protein kinase (AMPK), Wnt/β-catenin and estrogen receptor (ER) signaling; and (2) it can act indirectly by regulating insulin sensitivity, influencing tumor angiogenesis and modulating inflammatory responses by inhibiting NF-κB signaling[6,24,25]. On the contrary, leptin, a 167-amino acid pleiotropic adipokine that regulates food intake, energy expenditure, immunity, and inflammation[26,27], has been shown *in vitro* to promote growth and proliferation of neoplastic cells *via* activation of various growth and survival signaling pathways including canonical: Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3), phosphatidylinositol 3-kinase/v-Akt murine thymoma viral oncogene homolog/mammalian target of rapamycin (PI3K/Akt/mTOR), MAPK/Extracellular signal-related kinase 1/2 (ERK1/2) and non-canonical signaling pathways such as protein kinase C, c-Jun N-terminal kinase (JNK) and p38 MAPK[25-29]. Additionally, leptin may act indirectly by diminishing insulin tissue sensitivity causing hyperinsulinemia, by shifting inflammatory responses towards a T-helper 1 phenotype with oversecretion of pro-inflammatory cytokines and by influencing tumor angiogenesis; though such leptin effects were not seen *in vivo*[26,27]. Resistin, another pro-inflammatory adipokine synthesized predominantly in visceral macrophages in humans, is a 12 kDa cysteine-rich polypeptide[30-32]. Visfatin or nicotinamide phosphoribosyl-transferase (Nampt), a novel pleiotropic adipokine found in the visceral fat, acts as a pro-inflammatory cytokine, a growth factor and an enzyme in the cellular energy metabolism, particularly nicotinamide adenine dinucleotide (NAD) biosynthesis, which is required in a plethora of intracellular processes such as redox reactions, DNA repair, transcriptional regulation and activity of poly-ADP ribosyltransferases (PARPs) and deacetylases (sirtuins) modulating cell survival and cytokine responses[33-35]. The majority of epidemiologic studies has indicated that *in vivo* hyperresistinemia and hypervisfatinemia are associated with some obesity-related malignancies such as colon cancer, postmenopausal breast cancer and prostate cancer[7,31-34,36-42]; though their ontological role in the association between obesity and cancer needs to be clarified. Resistin and visfatin may: (1) upregulate pro-inflammatory cytokines *via* the NF-κB pathway[32,33]; (2) stimulate signaling pathways which are

important components of cancer-promoting machinery[32,33,41-43]; and (3) induct pro-angiogenic proteins such as the vascular endothelial growth (VEGF) and the expression of metalloproteases (MMPs) participating in tumor invasiveness and metastasis[32,33]. Much less is known about a novel pro-inflammatory adipokine, chemerin, which is found elevated in obese individuals[44]. Chemerin may cause IR in human skeletal muscle at the level of glycogen synthase kinase 3 (GSK3) and Akt phosphorylation, and glucose uptake. Finally, chemerin may activate signaling pathways pertinent to inflammation and cancer promotion, such as NF-κB, p38 MAPK and ERK 1/2[45].

Skeletal muscle, main myokines and cancer prevention

Skeletal muscle accounts approximately for 40% of body weight in non-obese individuals, constituting therefore the largest human organ[46]. There has been accumulating evidence that skeletal muscle is an important secretory organ producing several proteins and low molecular weight molecules[45,46]. Myokines are muscle-derived cytokines that exert autocrine/paracrine and endocrine effects. Myokines play a privotal role in metabolism as mediators of muscle-to-adipose tissue cross-talk and regulators of muscular glucose and fat homeostasis, and in cancer prevention as mediators of the beneficial effects of physical activity counteracting the harmful effects of pro-inflammatory adipokines[45,46]. It seems that the complex paracrine and endocrine interconnection between adipokines and myokines reflects a yin-yang balance with important implications in processes such as lipolysis control, insulin sensitivity and prevention from obesity-driven chronic low-grade inflammation and cancer promotion through anti-inflammatory adipokines and myokines. At the same time, skeletal muscle cells may secrete adipokines such as adiponectin, which can exert beneficial local metabolic effects enhancing insulin sensitivity and inhibiting inflammatory processes[47]. It is important to underscore that adipose tissue is not the exclusive source of adipokines. Although adipose tissue constitutes the primary site of adipokines production, several adipokines are synthesized by both fat and muscle, playing a critical role for autocrine/paracrine loops[45]. For example, IL-6 and IL-8 are considered adipokines but also myokines with different roles in inflammation, exercise, skeletal muscle development and insulin sensitivity.

It is well known that physical activity offers protection against a variety of chronic diseases including obesity, t2DM, CVD, osteoporosis, depression and cancer[45]. Recent meta-analyses and epidemiological studies have underscored the protective effect of physical activity on reducing colorectal, prostate and breast cancer risk by 20%-40%[45]. Interestingly, moderate-intensity physical activity after breast and colorectal cancer diagnosis may improve prognosis and reduce the risk of cancer-specific and overall mortality[48-51]. Below is discussed the role of major beneficial myokines.

IL-6 was the first described myokine produced in an exponential manner in response to muscle contraction after exercise in a strictly TNF-independent fashion[12,52]. IL-6 release from muscle is associated with exercise intensity and duration as well as muscle mass involved in the mechanical load[52]. Muscular IL-6 is involved in AMPK-mediated fat oxidation, skeletal muscle lipolysis and insulin-stimulated glucose uptake enhancing insulin sensitivity[12]. IL-6 also mediates some of the immunoregulatory and anti-inflammatory properties of regular exercise as it modulates TNF-α levels[52] and stimulates the secretion of classic anti-inflammatory cytokines such as IL-10 and IL-1ra[12]. In contrast to the beneficial effects of muscular IL-6, chronic elevated serum IL-6 levels synthesized by adipocytes and immune cells in the visceral adipose tissue are closely associated with *in vivo* IR, Mets, obesity and physical inactivity[12,45]. Interestingly, oncostatin M (OSM), a member belonging to the IL-6 superfamily, represents a pleiotropic myokine released by contracting myotubes[12]. OSM has been shown to exert *in vitro* important apoptotic effects on tumor cell lines by inhibiting proliferation in a variety of tissues comprising mammary epithelial cells, melanoma, ovarian and lung cells[12].

IL-15 is a 15 kDa myokine that is highly expressed in skeletal muscle especially after aerobic exercise and resistance, and acts as a myokine that inhibits adiposity[13]. Apart from its hypertrophic and anabolic effects on muscle tissue as an authentic myokine, IL-15 exerts many metabolic actions by enhancing glucose uptake and fat oxidation in muscle tissue, stimulating lipolysis and inhibiting preadipocyte differentiation and lipogenesis as part of the muscle-adipose cross-talk[13]. Obese individuals exhibit low plasma IL-15 levels[46]. Interestingly, IL-15 may stimulate the production of anti-inflammatory and anti-neoplastic adiponectin downregulating visceral obesity while it reduces white adipocyte size and serum leptin levels in male mice[12].

A new myokine, irisin, was recently discovered and named after the Greek messenger goddess Iris[46,53-55]. Physical activity increases the muscular expression levels of the transcriptional co-activator PGC-1α upregulating the expression of the type I membrane protein FNDC5, which is C-terminally cleaved and secreted into the circulation as irisin[53]. In turn, irisin increases the expression of uncoupled protein-1 (UCP-1) contributing to the "browning" of white adipose tissue characterized by enhanced mitochondrial density, oxygen consumption and non-shivering thermogenesis[55]. Therefore, the muscle-derived irisin exhibits beneficial metabolic actions by increasing energy expenditure, causing small weight loss and improving metabolic parameters such as insulin signaling and sensitivity[55]. Basal plasma irisin levels may increase in response to 10 wk of regular exercise in humans and correlate with physical activity levels both in

mice and humans[46,54,55].

INTERPLAY OF ADIPOKINES AND MYOKINES IN CANCER CACHEXIA

Almost 50% of patients suffering from advanced cancer stage present cachexia which is responsible for 25% of deaths due to cancer[14-16]. Cachexia is a complex metabolic state characterized by loss of skeletal muscle mass and adipose tissue leading to progressive functional impairment. Cachexia is usually associated with asthenia, anorexia, anemia, weight loss, hypoalbuminemia, IR and abnormal metabolism of carbohydrates, lipids and proteins[56]. Cancer cachexia may be caused by anorexia, dysphagia related to advanced esophageal cancer, an imbalance between protein synthesis and catabolism with an increase in energy expenditure, or a combination of the two[14-16]. However, the complex pathophysiology of cancer cachexia is based on the interplay between muscle and adipose tissue mediated by free fatty acids, various adipokines and myokines[14,15].

As cancer progresses, a variety of cytokines (IL-6 and TNF-α) and tumor-derived mediators such as proteolysis-inducing factor (PIF) and parathyroid hormone-related protein (PTHrp), activate the pro-inflammatory catabolic cytokine cascade and deactivate the anti-inflammatory anabolic network (IL-4, IL-10, IL-12 and IL-15) leading to a systemic, chronic inflammation in cancer patients[16]. Pro-inflammatory and pro-cachectic cytokines, mainly TNF-α, IL-6 and interferon-α, and a lipid mobilizing factor (LIF), which is homologous to the soluble plasma protein Zinc-α2-glycoprotein (ZAG), activate adipose triglyceride lipase (Atgl) triggering lipolysis which results in net mobilization of white adipose tissue and an augmentation of plasma free fatty acids levels[14,15]. Interestingly, ZAG, a recently identified 43-kDa adipokine, acts as a lipid-mobilizing factor stimulating lipolysis in adipocytes, and is enhanced in mice and humans with cancer cachexia[57,58]. Based on its lipid-mobilizing role, ZAG could also contribute to adipose tissue atrophy associated with cancer cachexia[58]. At the same time, the process of protein catabolism in cachexia starts and may be regulated by the cross-talk between adipose and muscle tissue mediated by free fatty acids, adipokines, cytokines and myokines. Interestingly, in cancer-bearing mice in which the *Atgl* gene is ablated, lipolysis is not activated and both adipose tissue mass and skeletal muscle mass are preserved[59]. TNF-α, named originally cachectin, presents a critical mediatory role in cancer cachexia. IL-6 and leptin may also inhibit synthesis and enhance lipid and protein catabolism in adipocytes and myocytes respectively[60]. Nevertheless, hypoleptinemia and hyperadiponectinemia characterize the cancer cachectic state in human studies[61,62]. Our group has shown that low leptin and elevated adiponectin levels were seen in pancreatic cancer cases compared to controls[62]. Hyperadiponectinemia may be a compensatory response to inflammation, IR and/or the disease-induced weight loss possibly through altering the size of adipocytes[62]. Besides, cachectic patients exhibit frequently a relative glucose intolerance and IR due to alterations in fat metabolism, hypoleptinemia, a pro-inflammatory state and an increased activity of the Cori cycle[16]. Muscle wasting in cancer cachexia mediated by free fatty acids, adipokines, cytokines and myokines results in: (1) an activation of the ATP-dependent ubiquitin-proteasome pathway which targets not only structural and sarcomeric proteins such as myosin, troponin and titin but also important myogenic transcription factors such as calcineurin and Myo D[63,64]; (2) a defective muscle regeneration capacity due to an abnormal regulation of satellite cells in skeletal muscle[14]; and (3) a hyperexpression of myokines that play an important role in muscle atrophy such as myostatin[65]. Muscle regeneration may be further compromised in cachexia due to the reprogramming of protein metabolism toward an increased production of acute phase response proteins sustained by the aminoacids secreted by skeletal muscle catabolism. In agreement with this concept, there is also evidence that TNF-α inhibits skeletal muscle regeneration *in vivo via* a caspase-dependent stem cell response[66]. Besides its role as a potent cachexia inducer, TNF-α may be a potent inhibitor of *in vivo* myogenesis[67].

Myostatin is a protein belonging to the transforming growth factor-β (TGF-β) superfamily, playing a pivotal role in the negative regulation of muscle growth and determining the size and mass of skeletal muscle[68]. Myostatin is an authentic myokine as it is exclusively produced by skeletal muscle and to a lesser extent by adipose tissue[65]. Deletion of myostatin in mice results in an increased number of satellite cells that are involved in muscle growth[65] leading to an enhanced muscle regeneration and skeletal mass hypertrophy and a reduction in total adipose tissue[46]. Physical activity attenuates myostatin expression, whereas myostatin deactivation may stimulate the beneficial effects of exercise on metabolism[46]. High myostatin gene expression and signaling enhancement have been associated with cancer cachexia[68]. In blood, myostatin is inhibited by its propeptide or other binding proteins such as follistatin, a hepatokine which belongs to the TGF-β superfamily[68].

Other myokines that could play a role in cachexia are Leukemia inhibitory factor (LIF), IL-7 and IL-8[46]. LIF, an IL-6 cytokine superfamily member that affects cell growth by inhibiting differentiation, represents a contraction-induced myokine acting in a an autocrine/paracrine manner to promote satellite cell proliferation for muscle regeneration. IL-7 and IL-8 are novel myokines participating in the regulation of skeletal muscle development[46]; however, their exact biologic functions remain unknown.

EMERGING PREVENTIVE AND THERAPEUTIC IMPLICATIONS

High-fat diet, weight gain and physical inactivity may

lead to visceral obesity and muscle loss, and consequently to the enhancement of a network of inflammatory pathways promoting the development of IR, Mets and malignancy growth. Physical activity offers protection against metabolic disorders and obesity-associated malignancies[45].

The capacity of adiponectin to stimulate insulin sensitivity synergistically with its apoptotic properties has rendered this adipokine a promising diagnostic and prognostic biomarker as well as a novel therapeutic tool in the pharmacologic armamentarium for treating cancer[3]. However, since adiponectin is extremely difficult to synthesize, research should be conducted in identifying pathways to augment endogenous circulating adiponectin levels in order to attenuate the obesity/physical inactivity-cancer connection[6].

Modulating adipokines and myokines could be a particularly attractive goal for cancer prevention, specifically in overweight/obese and physical inactive individuals. Regular moderate exercise, adoption of a balanced diet, weight reduction and bariatric surgery for morbidly obese persons may increase plasma adiponectin, irisin, IL-15 and the hepatokine follistatin[65], and decrease plasma leptin, resistin, visfatin, chemerin and myostatin concentrations, reducing thus the risk of developing cancer. Very recently, L-4F, an apolipoprotein peptide mimetic used for the pharmacologic upregulation of adiponectin, decreased multiple myeloma (MM) tumor burden through induction of apoptosis, increased survival of myeloma-bearing mice and provided protection against myeloma destructive osteolytic bone disease, an important clinical feature of MM[69]. Interestingly, MM as well as monoclonal gammopathy of undetermined significance which may subsequently progress to MM are characterized by hypoadiponectinemia[69,70]. ADP 355, a new adiponectin-based short peptide mimicking adiponectin action, decreased proliferation in several adiponectin receptor-positive cancer cell lines, modulated several key adiponectin signaling pathways and suppressed the growth of orthotopic human breast cancer xenografts by 31% *in vivo*[71]. Additionally, anti-Nampt (anti-visfatin) agents such as FK866, CHS-828 and APO866 inhibited tumor growth in a broad range of tumor cell lines by diminishing NAD levels, enhanced apoptosis or autophagy, and abrogated tumor growth in animal models of hematological malignancies without significant toxicity[33,72,73].

The pathway of IL-15 and irisin could be explored as a potential therapeutic avenue to combat disease states such as obesity and muscle loss, Mets and obesity-associated malignancies. Increased formation of brown fat instead of white fat has been shown to exhibit beneficial metabolic effects by improving glucose homeostasis and insulin sensitivity in multiple murine models[53-55]. Through regular physical activity, irisin and other myokines could ameliorate insulin sensitivity and attenuate the link between IR and cancer[46,52]. Exercise-induced myokines have been found to inhibit mammary tumor cell growth[12]. There is accumulating evidence that hyperinsulinemia, the hallmark of IR, and the increase of bioavailable IGF-I may promote cancer. Insulin exerts its oncogenic potential through enhancing growth factor-dependent cell proliferation and through abnormal stimulation of multiple cellular signaling cascades[74]. Recent data have consistently underscored the strong link between anti-diabetic treatment, which improves insulin sensitivity and adiponectin production, and decrease in cancer incidence and mortality[6,75].

Finally, the long-term beneficial effects of physical exercise on cancer prevention may be ascribed to the anti-inflammatory actions of myokines and adipokines[11,52]. The upregulation of pro-inflammatory cytokines *via* the NF-κB pathway in a chronic low-grade inflammatory disease state such as obesity is a significant component of the cancer-promoting machinery[6].

Regarding cancer cachexia, the metabolic dysfunction precludes the accretion of skeletal muscle mass, even if additional proteins and calories are provided. Furthermore, the use of anti-TNF (and anti-IL-6) antibodies against the main cachectic factor (TNF-α) in reversing cachexia has led to moderate results[16]. Due to the complex pathophysiology of cachexia, combined approaches to deactivate various pathways implicated in cachexia may open up a new era of significant therapeutic progress. In particular, targeting myostatin may represent a novel therapeutic strategy by using potential myostatin inhibitors such as soluble myostatin receptors, follistatin-related proteins, myostatin propeptide, anti-myostatin antibodies and small interfering RNAs[68]. Anabolic factors such as insulin-like growth factor I enhancing muscle precursor cell proliferation and regeneration are at the forefront of future therapeutic modalities for cachexia[16].

Nevertheless, more intensive basic research studies, *in vivo* animal studies, observational human studies, and larger prospective and longitudinal studies are needed in order to fully clarify the mechanisms underlying the effects of adipokines and myokines on cancer pathophysiology. Further studies are required for the development of reliable laboratory techniques (*e.g.*, enzyme-linked immunosorbent assays) to assess adipokines and myokines as well as their physiologic relevance. Which levels of adipokines and myokines should be considered abnormal needs also to be determined along with standardization of levels and assay procedures. Proteomics will identify new adipokines, myokines and the extent of the "adipo-myokinome".

Whilst understanding the interplay of adipokines and myokines with cancer might provide potential therapeutic targets, lifestyle amelioration remains the most important component in preventing obesity-related malignancies. Reduction of body weight, daily physical exercise and a balanced diet with fruit and vegetables consumption may improve energy balance and reduce the risk of developing IR, Mets, t2DM, CVD and obesity-associated malignancies. Advances in the field of translational in-

vestigation may lead to tangible benefits to obese and inactive persons who are at increased risk of cancer as well as to cancer patients with cachexia.

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