Adipose tissue, obesity and adipokines: role in cancer promotion

Abstract: Adipose tissue is a complex organ with endocrine, metabolic and immune regulatory roles. Adipose depots have been characterized to release several adipocytokines that work locally in an autocrine and paracrine fashion or peripherally in an endocrine fashion. Adipocyte hypertrophy and excessive adipose tissue accumulation, as occurs during obesity, dysregulates the microenvironment within adipose depots and systemically alters peripheral tissue metabolism. The term “adiposopathy” is used to describe this promotion of pathogenic adipocytes and associated adipose-related disorders. Numerous epidemiological studies confirm an association between obesity and various cancer forms. Proposed mechanisms that link obesity/adiposity to high cancer risk and mortality include, but are not limited to, obesity-related insulin resistance, hyperinsulinemia, sustained hyperglycemia, glucose intolerance, oxidative stress, inflammation and/or adipocytokine production. Several epidemiological studies have demonstrated a relationship between specific circulating adipocytokines and cancer risk. The aim of this review is to define the function, in normal weight and obesity states, of well-characterized and novel adipokines including leptin, adiponectin, apelin, visfatin, resistin, chemerin, omentin, nesfatin and vaspin and summarize the data that relates their dysfunction, whether associated or direct effects, to specific cancer outcomes. Overall research suggests most adipokines promote cancer cell progression via enhancement of cell proliferation and migration, inflammation and anti-apoptosis pathways, which subsequently can prompt cancer metastasis. Further research and longitudinal studies are needed to define the specific independent and additive roles of adipokines in cancer progression and reoccurrence.

Keywords: adipocytokines; adiposity; cancer progression; cancer reoccurrence; cell lines; human; rodent.

Introduction

Adipose tissue was formerly characterized to have limited physiological roles mainly pertaining to energy storage following nutrient excess and insulation to protect from cold temperatures. Currently it is recognized that adipose tissue is a complex organ with endocrine, metabolic and immune regulatory roles. Adipose depots have been characterized to release over 20 hormones and signaling molecules termed “adipokines” or “adipocytokines” that work locally in an autocrine and paracrine fashion or peripherally in an endocrine fashion. Adipose tissue was formerly characterized to have limited physiological roles mainly pertaining to energy storage following nutrient excess and insulation to protect from cold temperatures. Currently it is recognized that adipose tissue is a complex organ with endocrine, metabolic and immune regulatory roles. Adipose depots have been characterized to release over 20 hormones and signaling molecules termed “adipokines” or “adipocytokines” that work locally in an autocrine and paracrine fashion or peripherally in an endocrine fashion. Under normal conditions, adipocytokines function to regulate numerous physiological processes that play an overall role in appetite and energy balance such as, but not limited to, lipid metabolism, glucose homeostasis, insulin sensitivity, angiogenesis, blood pressure and inflammatory processes. In obesity, however, adipocyte hypertrophy and excessive adipose tissue accumulation, termed “hyperplasia”, dysregulate the sensitive microenvironment within adipose depots, which consequently alters their physiological processes. This action causes “adiposopathy”, which is the promotion of pathogenic adipocytes and adipose tissue related disorders.

Obesity-associated diseases are a rapidly growing concern of national and international public health. In particular, obesity is highly associated with heightened risk of several chronic illnesses including cancer development, reoccurrence and death. It has been estimated that roughly 20% of all cancers are caused by excess weight gain, however this percent is proposed to be an underestimation [1, 2]. In addition, cancer survivors with higher body mass index (BMI) have a greater cancer reoccurrence risk [3]. Epidemiological observation also supports that Americans with a high BMI have a significant increase in risk of dying from cancer than those with average BMI [1, 4]. Common cancers that run a greater risk of occurrence/prevalence with increased adiposity include, but are not limited to prostate, colon, breast, ovarian, endometrial and...
pancreatic. Prostate cancer in obese men is demonstrated to be more aggressive when compared with normal weight individuals [5]; consequently, obesity increases the risk of prostate cancer mortality [6]. A reduction in body mass, however, is proposed to reduce the risk of prostate cancer [5]. Although colon cancer readily occurs in both men and women, the associated obesity risk with this cancer is greater in men than women, hence studies suggest that obesity increases the risk of colon cancer death in men only [7, 8]. In women, obesity-associated cancer risks are commonly attributed to weight accumulation that occurs post-menopause. Postmenopausal obesity is a predictor of fatal breast cancer [9] and increased risk for endometrial cancer [10] and ovarian cancer [11]. Much like the other cancers, obesity also increases pancreatic cancer risk [12, 13]. Other studies indicate, however, that weight loss—in particular that accompanying with gastric bypass—is associated with reduced cancer risk when compared to those without surgery [14]. This data supports recommendations of weight loss to reduce cancer risk.

There are several proposed mechanisms that link obesity/adiposity to high cancer risk and mortality such as, but not limited to, obesity-related insulin resistance, hyperinsulinemia, sustained hyperglycemia, glucose intolerance, oxidative stress, inflammation and/or adipokine production. Several epidemiological studies have demonstrated a relationship between specific circulating adipokines and cancer risk; these studies will be discussed below. In general, diseases including cancer are proposed to be more prevalent during obesity because adipose tissue dysregulation that occurs with excessive lipid accumulation induces chronic systemic low grade inflammation. During obesity, the paracrine loop between adipocytes and immune cells becomes dysregulated because most adipokines significantly increase and consequently alter immune cell cytokine secretion. Overall, adipose tissue is a highly involved mediator of the inflammatory immune system response. Enhanced secretion of adipose-derived hormones, growth factors and pro-inflammatory cytokines are major factors in the pathogenesis of tumor growth, increased cell migration and subsequently cancer metastasis.

**Leptin**

The human leptin gene *LEP*, also known as the *ob* gene, encodes a protein that is 16 kDa in weight and 167 amino acids long [15]. It was isolated in 1994 by Jeffrey Friedman [15] and has since been dubbed “the hunger gene” because of its primary action to regulate food intake and energy expenditure. The peptide hormone is secreted from adipose tissue in proportion to an individual’s fat mass and exerts its effects via blood circulation with targets such as the central nervous system, muscle, liver and adipose tissue [16]. The discovery of leptin was seminal in redefining adipose tissue as an endocrine organ, which discredited traditional views suggesting it was just an inert lipid storing tissue.

Leptin binds to leptin receptors encoded by *LEPR*, also called the *db* gene, which has six isoforms (*ObRa-ObRf*) belonging to the family of cytokine receptors. The long form *ObRb* is a single transmembrane protein that is expressed throughout the central nervous system (CNS), but its function is most relevant in the hypothalamus [17]. Of the short forms identified, *ObRa* and *ObRc* are active in most tissues throughout the body [17]. Leptin and its long form receptor act in the fed state on appetite and metabolism through stimulation of proopiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) or suppression of neuropeptide Y/AgRP [18], these alterations ultimately result in an increase of α-melanocyte-stimulating hormone. The fasted state induces decreases in leptin concentration that subsequently reverse the above actions in the CNS [18]. As leptin binds to its receptors in either the CNS or periphery, it induces Janus kinase 2 (JAK2) to phosphorylate tyrosine resides on the cytosolic domain. Once JAK2 is activated, multiple downstream pathways are stimulated, including the signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K) pathways [19], which regulate gene expression, cell growth, and inflammation.

Resistance to leptin is one of the hallmarks of obesity and is proposed to contribute to the many co-morbidities of the metabolic syndrome. Circulating levels in a normal lean individual are 5–15 ng/mL, whereas with obesity these levels can reach 100 ng/mL and exceed 250 ng/mL in the morbidly obese [20]. High circulating leptin concentrations, known as “hyperleptinemia”, interfere with intracellular signaling by increasing the transcription of SOCS3 (suppressor of cytokine signaling) [21], which ultimately thwarts further signaling cascades. It is also proposed that obesity causes a reduction in blood-brain barrier transport, which reduces accessibility of leptin to the hypothalamus [21]. Overall, leptin resistance leads to dysregulated cytokine signaling, reduced appetite suppression and energy expenditure, which perpetuates inflammation and subsequently further increases adiposity and its associated co-morbidities [22].
It is well-established that obesity is a highly associated risk factor for cancer, hence as BMI increases so does the relative risk of many types of cancer [1]. Epidemiological studies indicate increased circulating levels of leptin, as occurs during obesity, and are associated with cancers such as breast [23] and colorectal [23, 24]. Leptin has also been studied in vitro on cancer cells and is implicated in proliferation of breast, colon, prostate, pancreatic, ovarian, and lung cancers [25]. Indeed, research suggests that leptin plays a role in the progression of mammary tissue tumorigenesis via its function as a growth hormone [26]. Upon binding and activation of JAK2, STAT3 is phosphorylated and dimerizes, causing the transcription factor to translocate to the nucleus where it upregulates genes involved in cell cycle, anti-apoptosis (cell survival), cell invasion/migration, angiogenesis, and inflammation [27].

The general effects of leptin in cancer research include proliferation, cell survival, angiogenesis, and subsequent cancer progression. For the most part, proliferation of cancer cells occurs through activation of the STAT3, ERK, and PI3K signaling pathways that stimulate growth and cell cycle genes [25]. The mechanisms of cell survival are related to an inhibition of apoptosis mediated by upregulation of Bcl anti-apoptotic genes [28]. Angiogenesis occurs through vascular endothelial growth factor (VEGF), which is stimulated by HIF-1α and NFκB, as shown in 4T1 mouse mammary cells [29]. Leptin and its receptor are overexpressed in cancer cells, particularly epithelial cells lining certain tissues. This pathway is responsible for cross-talk between leptin and oncogenes to facilitate in tumor growth and impaired cell death. Specifically, the VEGF gene is induced by leptin and stimulates angiogenesis to support tissue expansion by allowing oxygen to reach proliferating cells [30]. Another downstream effect of JAK2 activation is the MAPK or ERK – extracellular signal regulated kinase (ERK) pathway [31]. The ERK phosphorylation cascade results in activation of transcription factors that interact and bind to serum response elements in the promoter region of the c-fos gene required for cell division [32]. Also, following JAK2 activation is initiation of PI3K [31] and Akt phosphorylation, which stimulates glucose utilization, cell growth via mTOR, cell proliferation and differential apoptosis [33]. Once carcinogenesis occurs, tissue cells release signaling molecules, including leptin, in a paracrine and autocrine manner [34]. To summarize the effects of leptin, its properties include anti-apoptotic, pro-angiogenic, mitogenic, and pro-inflammatory, all supporting tumor growth and cancer progression.

Leptin is shown to be overexpressed in ductal breast tumors, contributing to a proliferative effect, while it is unexpressed in healthy breast tissue not in the vicinity of tumor growth [35]. The role of leptin in tumor growth is demonstrated via mice cancer models. More specifically, MMTV-Wnt-1 mice, a model of mammary tumor growth, that are obese but leptin deficient, have suppressed mammary tumor growth and decreased tumor cell survival compared with those that are leptin sufficient [36]. Leptin acts as a growth hormone in the MCF-7 breast cancer cell line through an increase in aromatase via ERK and STAT pathways [37], as well as enhanced DNA binding of the AP1 transcription factor [37]. Indeed, increases in aromatase activity were demonstrated in cultured breast cancer cells following leptin incubation, however this did not occur if cells were treated with an aromatase inhibitor [37]. Recent findings on the strong relationship of adipocyte-derived leptin with breast cancer has lent itself to being a target of treatment.

Research also proposes that obesity-induced increases in circulating insulin can enhance the effect of adipose-derived leptin on breast cancer progression. Obesity is characterized by both hyperinsulinemia and increases in circulating leptin. In breast cancer cells, insulin has been demonstrated to stimulate leptin receptor expression, thus increases in insulin along with adipocyte-derived leptin act accumulatively to induce cancer progression [38]. In breast cancer cells, the leptin activity is enhanced following treatment with insulin, which acts via the ERK and PI3K pathways [38]. Transcription factors required for the insulin-mediated increase in leptin expression include Sp1, involved in cell growth and HIF-1α, a response to hypoxia [38].

Breast cancer patients with high circulating levels of leptin are also more susceptible to further cancer cell progression. Leptin is proposed to act initially on breast epithelial cells, transforming them into malignant forms that affect surrounding cells in a paracrine fashion to mediate further cancer cell proliferation [39]. Moreover, addition of leptin to MCF-7 breast cancer cells decreases the expression of the cancer suppression protein p53, exploiting cancer cell survival property [40]. In a female transgenic mouse model susceptible to mammary tumor growth, deficiency of either the leptin gene (ob/ob) [41] or its receptor (db/db) resulted in no development of mammary tumors, whereas tumors were detected in over half of the controls [42].

Leptin has been identified as a biomarker for gastro-oesophageal patients who fail to respond to therapy. Treatment effectiveness is extremely variable in these individuals and greatly affects prognosis and survival [43]. Patients with higher levels of leptin mRNA expression are less responsive to treatment, while those with low levels were more likely to survive [43]. Therefore, leptin
levels can be used as an indicator of tumor responsiveness and help guide treatment options to improve a patient’s outcome.

Leptin is expressed in colorectal tumors with a greater expression in more aggressive tumors (more histologically differentiated tumors) [44]. The contribution of leptin to colorectal cancer growth has not been established at this point, however leptin gene expression is regulated by HIF-1α induced by hypoxia [44].

Liver cancer cells HepG2 have been demonstrated to be sensitive to leptin treatment where leptin promotes cell growth and prevents cell death through its unfolded protein response [45]. Both proliferation and survival are aided by inhibition of ER stress signals, which is a regulatory pathway for apoptosis [45]. Both PERK and caspase 12 are implicated in inadvertent cell survival and enhanced proliferation [45]. In the inflammatory condition of hepatitis C virus, human hepatocellular carcinomas (HCC) arise and LEPR has been identified as the most mutated gene in the affected tissue resulting in reduced phosphorylation of STAT3 [46]. Impairment in STAT3 is demonstrated to contribute to enhanced tumorigenesis [46]. Furthermore, patients with hepatitis B virus who have specific single nucleotide polymorphisms Lys109Arg or Gln223Arg in the leptin receptor gene were shown to have differential risk of HCC [47].

There are clear associations between obesity, leptin and cancer in various tissues. Though the mechanisms are not fully understood, increased circulating levels of leptin and the downstream effects of its receptor contribute to tumor growth and progression. Figure 1 includes a general model of the best characterized pathways of leptin and its relation to cancer progression.

**Adiponectin**

The hormone adiponectin is secreted exclusively from adipose tissue and is the only adipokine with an inverse relationship to fat mass. It is encoded by the gene AdipoQ, makes a protein 244 amino acids in length that is 30 kDa in weight [48]. Adiponectin is involved in glucose and lipid homeostasis and is therefore implicated in the pathogenesis of insulin resistance [49] and diabetes [50]. Adiponectin was discovered in the mid-1990s as a requirement for

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**Figure 1**: Leptin is increased with obesity.
Leptin binds to its receptor and initiates phosphorylation of JAK2 on its cytosolic domain. Ras/Raf signaling is activated and induces mitogen-activated protein kinase activity, including cell cycle inducers and inactivation of tumor suppressor protein p53. STAT3 binds to phospho-tyrosines on receptor and translocates to the nucleus to activate transcription of cell proliferative genes. Activation of phosphoinositide 3-kinase (PI3K) leads to AKT/mTOR stimulation promoting cell growth and survival.
Adipocyte differentiation of 3T3-L1 cells and its secretion is correlated with insulin sensitivity [48]. Plasma concentrations of this hormone range from 2 to 20 μg/mL [51].

Adiponectin acts through its receptors, AdipoR1 and AdipoR2 [52], which are transmembrane receptors that activate a signaling cascade upon ligand binding [53]. AdipoR1 is found mostly in skeletal muscle, but also appears in the hypothalamus, liver, and other tissue [54]. It stimulates the AMP-activated kinase pathway both directly and through an influx of extracellular calcium leading to factors that affect lipid and glucose metabolism [54]. AdipoR2 is commonly found in liver tissue and appears also within white adipose tissue and the vasculature [54]. This isoform affects PPARα activity, which regulates lipid metabolism through gene transcription and increased expression of its ligands [54]. Adiponectin receptors also have ceramidase stimulatory activity, which lowers intracellular ceramide, increases sphingosine 1-phosphate levels, and protects against apoptosis [55].

Obesity is associated with lower plasma adiponectin levels [56] as well as decreased expression of its receptors AdipoR1 and AdipoR2 [57]. Blood plasma levels are not only reduced in obese individuals, but also in non-obese individuals with related conditions such as type 2-diabetes and cardiovascular disease [58]. Adiponectin has been recognized as an insulin-sensitizing hormone that works by decreasing liver and muscle triglyceride content through increased AMPK activity and expression of energy expenditure molecules [59]. Hence this hormone has similar properties of exercise in that it increases glucose uptake in muscle and suppresses glucose production in liver.

Adiponectin is one of the only adipocyte-secreted protein with beneficial effects on health and disease due to its role in lipid metabolism and glucose homeostasis. When adiponectin is decreased with obesity, known as hypoadiponectinemia, as the result of increased secretion of other cytokines like TNFα, its anti-disease properties are also dampened [60]. As the most prolific protein secreted by adipocytes, adiponectin is anti-inflammatory, pro-apoptotic, and anti-proliferative under normal circumstances [60]. There are two ways the hormone can effect cancer retardation: either directly on the tumor cells or through its insulin-sensitizing effects [61]. Either way, decreases in adiponectin have been associated with breast, endometrial, colon, esophageal, and liver cancer among many others [61].

Actions of adiponectin in breast cancer lines that express AdipoR1/R2 include reduce cancer invasion and migration to other cells [62]. Research demonstrates adiponectin is anti-carcinogenic in breast cancer cell lines, including MCF-7, MDA-MB-231 and T47D through its anti-proliferative properties [63]. In all three cancer cell lines mentioned above, adiponectin increases activation of cell apoptosis and inhibits the cell regulatory cycle [64–66]. Others also demonstrate adiponectin pre-treatment significantly attenuates mammary tumor growth and tumor weight in mice injected with the human breast cancer cells MDA-MB-231 [67]. In a human breast cancer cell study, in vitro exposure of MCF-7 cells to adiponectin-induced phosphorylation of AMPK, which subsequently hindered cell cycle progression through decreased expression of cyclin D1 and c-myc mRNA expression, and stimulated apoptotic responses through increased expression of p53 and Bax [64]. Adiponectin also reduces the bioavailability of certain growth factors, such as platelet-derived growth factor BB (PDGF-BB), basic fibroblast growth factor (FGF), and heparin-binding epidermal growth factor-like growth factor (HB EGF) [68]. Therapeutic targets of breast cancer include therapies that activate the signaling or mimic the actions of adiponectin such as Metformin, PPARγ agonists and activators of AMPK signaling pathway [62].

Decreased adiponectin receptor expression is associated with a histological higher grade of endometrial cancer [69]. Hence, adiponectin receptor expression decrease is a proposed contributor to cancer progression and currently is a proposed target of treatment for endometroid adenocarcinomas [69]. In one study, KLE and RL95–2 human endometrial cancer cell lines had a decrease in proliferation when incubated with adiponectin [70]. If adiponectin receptors, however, were repressed in the same cancer lines, the protective effects of adiponectin were reduced [70]. These results suggest a reliance on receptors adipoR1 and adipoR2 in the inhibitory effects of adiponectin on endometrial tumor cell progression [70]. LKB1 was identified as a tumor suppressor gene required for adiponectin-mediated AMPK activation in KLE and RL95–2 endometrial cancer cell lines [70]. Consistent with this, a cohort of 60 patients with endometrial cancer had significantly lower serum adiponectin levels than controls [71]. Taken together, decreased expression of the protective adiponectin hormone is a risk factor for endometrial cancer in postmenopausal women.

Adiponectin and plasminogen activator inhibitor-1 (Pai-1) are known mediators of colorectal cancer progression. The two proteins are inversely regulated in both the early and late stages of adipocyte differentiation [72]. During early stages of 3T3-L1 cell differentiation, activation of PPARγ or reduction of Pai-1 causes an
increase in adiponectin and AMPK activity [72]. This shows that treatment with adiponectin may modulate the poor prognosis of colorectal cancer patients associated with increased Pai-1 levels [72]. Aside from treatment possibilities, adiponectin is a good biomarker for colorectal adenoma patients due to its significant inverse correlation with the number of adenomas [73]. Additionally, low adiponectin levels are associated with insulin resistance as well as stage of colorectal cancer, indicating that low adiponectin is connected to poor prognosis and possibly carcinogenesis [74]. Furthermore, in both human and mouse colon cancer cell lines adiponectin and Metformin combined reversed the effect of IL-1β, an inducer of cancer carcinogenesis via tumor suppressor protein p53 [75].

Taken together, high adiponectin levels have attenuating effects on cancer expression and progression. Its inverse relationship with fat mass supports adiponectin’s role in cancer as it relates to obesity and weight status. Figure 2 includes a general model of the best characterized pathways of adiponectin and its relation to cancer progression.

Apelin

Apelin is a peptide hormone discovered in 1998 that functions as a ligand for the G-protein coupled receptor APJ [76]. It is expressed in many tissues throughout the body and ranges between 13 and 36 amino acids with intended target receptors that include the CNS [76]. Apelin produced and secreted by adipocytes has been demonstrated to have effects ranging from fluid homeostasis, insulin secretion, epithelial proliferation, and cytokine regulation [77, 78]. This hormone is proposed to be anti-obesigenic in normal weight individuals and behaves similar to that of insulin, however levels are found to be increased in obese individuals as well as those with type 2-diabetes [79]. The true role of apelin, however, is unclear as it exhibits opposing effects on energy metabolism with respect to peripheral vs. central tissue [79]. Due to the ability of apelin to increase glucose uptake and decrease insulin resistance and adiposity in the periphery [79], it is an attractive target for control of body weight and metabolic disorders.

In regards to cancer, apelin had been demonstrated to play a role in lymph node metastasis and

Figure 2: Adiponectin is decreased with obesity. Translation of protein synthesis S6K/eIF4E and cell cycle genes as well as angiogenesis via mTOR pathway is blocked by activation of the AMP-activated protein kinase (AMPK). Cell growth and proliferation factors initiated by the insulin-induced PI3K pathway is also blocked via AMPK. Anti-apoptotic and migratory proteins induced by p65/p50 of the NFkB pathway is inhibited by peroxisome proliferator-activated receptor-alpha. Adiponectin receptors exhibit ceramidase enzymatic activity to reduce detrimental effects of intracellular ceramide accumulation.
lymphangiogenesis via binding to its receptor in lymphatic endothelial cells that activates ERK and P38 pathways, leading to cell proliferation, migration, and cell survival [80]. In addition, in a study of females with endometrial cancer, apelin levels were significantly higher in the obese group than non-obese controls and was positively correlated with fasting insulin levels, suggesting that high circulating levels of apelin associated with obesity is a risk factor for endometrial cancer [81].

Visfatin

Visfatin a small molecule of 52 kDa was originally identified as Pre-B-cell Colony enhancing factor (PBEF) by Samal et al. [82]. Nampt, discovered even earlier by Preiss et al. in 1957 [83], was similar to PBEF and visfatin, but was not well characterized at the time of discovery. The connection that PBEF and Nampt were the same molecule was later made by Rongvaux et al. [84]. Nampt would later be renamed visfatin, which is essentially the same molecule as PBEF. This molecule plays several biologically significant roles, including immune cell signaling, insulin mimetic effects, and regulation of the NAD biosynthetic pathway. Nampt is the enzymatic form, capable of catalyzing biosynthetic reactions, of the molecule that plays an important part in the biosynthesis of NAD as it is the rate-limiting enzyme [84, 85]. This enzyme is important both in regulation of cellular energetics and the control of other enzymes dependent upon NAD for their functions [86]. PBEF is another recognized form of the visfatin molecule that functions as a cytokine produced and secreted by cells of the immune system, leukocytes, which stimulate the expression of a number of pro-inflammatory cytokines including TNF-alpha, IL-1β, and IL-6 and promote the differentiation of B-cells [82, 86]. The final form, visfatin, was discovered to be secreted from mainly visceral adipose tissue cells and has the ability to function similarly to insulin [87]. Recent studies, however, demonstrate that visfatin may be more heavily expressed in macrophages that infiltrate adipose tissue [88]. Therefore the macrophages are proposed to release visfatin in response to inflammatory signals rather than the adipocytes excreting it themselves [88].

It has been somewhat controversial as to the role that visfatin may actually be playing in obesity. However, mounting evidence suggests that there is indeed an association between obesity and increased visfatin levels in the body. In a recent meta-analysis by Chang et al. [89], they observed a positive correlation between visfatin and insulin resistance as well as elevated visfatin levels association with obesity, adiposity, metabolic syndrome, type 2 diabetes and cardiovascular disease. Another recent analysis by Jurdana et al. [90] also showed higher baseline levels of visfatin after fasting in overweight and obese subjects than those in controls. The association of visfatin and obesity is of importance to consider as it has been demonstrated that obesity is a significant risk factor for cancer development [1, 91–93].

Current studies propose that visfatin is involved in the development and pathophysiology of a number of different cancers. The relation of visfatin to colorectal cancer (CRC) is among the best characterized to date [94–96], but data supporting its role in breast cancer or post-menopausal breast cancer (BC/PBC) is increasing [97]. Research also demonstrates a role of visfatin in ovarian cancers [98]. The role of visfatin in the development of the previously mentioned cancers has been attributed to several possible mechanisms. First, visfatin can directly induce the production of inflammatory cytokines, such as IL-6, however the receptor that mediates this particular pathway is currently unknown [99]. In addition, increases in visfatin are directly associated with increases in TNF via Sirt6 [100]. Sirt6 is an NAD-dependent enzyme that acts post-transcriptionally in the upregulation of TNF [100]. This links Nampt and levels of NAD to the inflammatory response that can affect promotion of carcinogenesis [98, 100]. The control of TNF and Sirt6 by NAD levels provides a potential link to carcinogenesis by Nampt via a metabolic mechanism. A second mechanism that links visfatin to increased cancer risk is its role in enhancing cancer cell survival. Specifically, CRC cells express chemokine receptors, CXCR4 and CXCR7, both of which can bind SDF-1 that promotes survival and migration of the cancerous cells [101, 102]. Wen-Shih Huang et al. [96] demonstrated that increased production of visfatin leads to increased expression of SDF-1. This is mediated by the B1 integrin and involves signaling through the ERK and p38 MAPK pathways [96]. ERK and p38 MAPK signaling lead to an increase in NF-KB and AP-1, leading to the increased expression of SDF-1 and increased CRC cell survival and migration [96]. Inhibitors of NF-KB and AP-1 effectively decreased the expression of SDF-1 [96]. A third pathway recently identified involves redox pathways and the reduction of reactive oxygen metabolites by visfatin through increased activity of antioxidative enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSHPx). Hence, this visfatin
pathway induces cancer cell protection from cytotoxic damage of reactive oxygen species [103]. This was demonstrated in cultured human melanoma cells (Me45) where visfatin treatment increased activity of the antioxidative enzymes [103]. Therefore, in an apoptotic state increases in visfatin induce antioxidative activity, which results in increased viability of the cancer cells. This suggests that increased levels of visfatin are protective against oxidative damage in both normal cells and existing cancer cells, thus protecting them from apoptosis and allowing for survival and proliferation [103].

The last mechanism involves the enzymatic activity of Nampt and the generation of NAD. NAD synthesis is required for many cellular functions but mechanisms specifically applicable to cancer progression include those involved in cell growth and survival, DNA repair, and angiogenesis [98]. Among the best characterized cancer-inducing cellular functions regulated by Nampt is the regulation of gene transcripts. An increase in Nampt expression leads to an increase in cell survival and Sirt1 activity, increasing angiogenesis [98]. Based on this outcome, Shackelford et al. [98] tested Nampt expression in ovarian serous adenocarcinomas (OSAs) that exhibit a high level of Stat3 expression, which leads to an increase in Nampt levels. The upregulation of Stat3 was demonstrated to be through IL-6 signaling [104]. In this manner it may actually be possible for visfatin to trigger the release of IL-6 that is responsible for the upregulation of Stat3 [104] that in turn increases endogenous Nampt levels [98]. It was also demonstrated that the Nampt levels were indeed significantly increased in the OSAs compared to controls [98]. Figure 3 depicts the best characterized cancer progression pathways induced by visfatin also known as Nampt and PBEF.

![Figure 3: Visfatin is increased with obesity.](image)

Shown are three distinct mechanisms in which visfatin exerts effects on cancer. First it was shown that visfatin can stimulate monocytes to release the inflammatory cytokine IL-6. IL-6 then signals in an intracellular fashion to increase the expression levels of Stat3 which upregulates the active enzymatic form of visfatin, Nampt. Nampt can then cause increased cell survival through Sirt-1, and Sirt-6 stimulates the release of TNF-α, an inflammatory cytokine that has been linked to carcinogenesis in states of chronic low grade inflammation such as obesity. In the second pathway, visfatin signals through the cell surface receptor, Beta-1 integrin. This binding of ligand signals the upregulation and activation of MAPKs p38 and ERK. The MAPK cascades increase the expression of Ap1 and NFκB transcription factors that then upregulate SDF-1, leading to increased survival and migration in a cancer cell model. The third pathway was demonstrated through the action of visfatin on Me45 cancer cells. Treatment caused an increase in the antioxidative enzymes SOD, CAT, and GSH-PX via an unknown receptor. The increase in the enzymes was speculated to lead to a decrease in cell death by ROS and thus a protective effect on cancerous cells.
Resistin

The human gene RETN is responsible for the coding and production of resistin, a small molecule adipokine of roughly 12.5 kDa [105]. Resistin was discovered by Steppan et al. [105] and subsequently named in a paper published in 2001. As an adipokine it was initially considered to mainly be a link between obesity and insulin resistance and was thought to be more heavily secreted by adipocytes as was demonstrated in rodents [105]. As discovered in the mouse model, it was shown that resistin circulates in the serum and is increased in both genetic and diet induced obesity [105]. It was also demonstrated that neutralization of resistin, by way of antibody binding, improves blood glucose levels and insulin sensitivity [105]. Recent studies in humans have indicated that unlike rodents, resistin is heavily expressed in peripheral mononuclear cells, but minimally expressed in adipocytes and preadipocytes [106]. Based on resistin being more highly expressed in immune cells that infiltrate the adipose tissue, Lerkhe et al. [107] demonstrated that the levels of resistin were more likely related to the inflammatory status of the individual. For this reason it has been hypothesized that resistin may be one of the adipocytokines that heavily influences the development of cancers. It has been demonstrated that resistin may represent the link between obesity and an increased inflammatory state and the influence that inflammation then exerts on the development of tumors [108].

RESTIN

Restin has been investigated in a number of cancers including colorectal [73, 95], breast [109], and prostate cancers [110], and HCC [111]. Specific cascades that link resistin to cancer include signaling through TLR4 and the induction of the PI3K signaling cascade, and stimulation of NF-kB [112, 113]. Activation of these pathways can cause a spiraling cascade of cytokines that continually upregulate inflammatory responses and perpetuate an increased inflammatory state that can lead to a carcinogenic state [112, 113]. The downstream pro-inflammatory cytokines produced activate specific pathways that lead to proliferation, differentiation and metastasis of the cancerous cells as seen by the activation of JAK/STAT and MAPK pathways via IL-6 that is upregulated by NF-kB [114]. PI3K and AKT phosphorylation are also induced by resistin and lead to the proliferation of cancer cells as demonstrated in several cancer cell lines [110].

Another mechanism of action for resistin in relation to gastric cancer was discovered to be similar to that previously discussed with visfatin. Gastric cancer cells treated with resistin have increased expression of SDF-1 [115]. Binding of resistin to the TLR-4 receptor induces signaling via the p38 MAPK and NF-kB pathways, which subsequently leads to the upregulation of SDF-1 [115]. The major difference between the visfatin and resistin pathways is the receptor that mediates the signaling cascades responsible for the upregulation of SDF-1. Specifically, visfatin binds to B1 integrin whereas resistin binds to TLR-4. Another signaling pathway for resistin recently defined is related to promotion of cell survival through activation of PI3K/AKT signaling pathways [110], which promotes cell survival by inactivating pro-apoptotic proteins via phosphorylation [110]. A major aspect and critical step of tumor metastasis is enhanced cell adhesion to the endothelium [116, 117]. Two important molecules that are involved in this process are the intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [118]. It was recently demonstrated that resistin mediates expression of these molecules on Sk-Hep1 cancer cells, thus tumor cell adhesion to the endothelium is regulated by resistin [111]. It was also demonstrated that blocking the generation of NF-kB effectively blocked the upregulation of the two adhesion molecules [111].

A number of mechanisms have been indicated for the involvement of resistin in the pathogenesis of cancer. As discussed, many of these mechanisms are triggered through an intracellular signaling cascade and many flow through NF-kB. Downstream effects are seen in increases in the inflammatory profile and immune cell recruitment, changes in expression of adhesion molecules and production of cellular products that help to increase survival, differentiation and metastasis of the cancer cells themselves. A summary of the best characterized pathways of the role of resistin in cancer progression are depicted in Figure 4.

Chemerin

Expression of the mature/active form of chemerin, a 16-kDa protein, was originally characterized in human tissues such as the spleen, lymph nodes and lung [119]. Within these tissues, chemerin is proposed to be a mediator of antitumor immunity and immune surveillance by functioning as a chemoattractant for immune cells, including natural killer, macrophages and dendritic cells [119–121]. In 2007 it was discovered that chemerin and its associated receptor, CMKLR1, were also highly expressed in isolated human and mouse adipocytes [122] suggesting that adipose tissue is a source and target for chemerin signaling. Adipocytes have been demonstrated to secrete physiological amounts of chemerin in early adipocyte differentiation and as the cells mature this adipokine
is increasingly secreted [122]. Adipose-tissue-derived chemerin acts in both an autocrine and paracrine manner. Under normal physiological circumstances the autocrine chemerin pathway in adipocytes regulates elements critical in the early events of adipogenesis, hence knockdown of chemerin or CMKLR1 in preadipocytes greatly inhibits subsequent differentiation to mature adipocytes [122]. In mature adipose tissue the autocrine response of chemerin is linked to modulating metabolic pathways of lipolysis, glucose uptake and lipostatic signaling [122]. The paracrine response of adipocyte release chemerin is described to be predominately active during an inflammatory process such as chronic low grade inflammation associated with obesity. Specifically, excessive lipid accumulation induces adipose tissue hypoxia and increases free fatty acid release, adipokine secretion and metabolic dysregulation [123]; these alterations consequently activate an inflammatory response. Like many adipokines, increases in plasma chemerin concentration are highly associated with increases in BMI and metabolic syndrome [124]. The contribution of adipose tissue secreted chemerin to the progression of pathophysiology of obesity and metabolic dysregulation is proposed to stem from its role in local pro-inflammatory response. Indeed, CMKLR1 is significantly expressed in immune cells such as neutrophils, activated macrophages and dendritic cells [119]. It is suggested that increases in adipocyte-derived chemerin, as occurs in obesity, induce local paracrine inflammatory response by enhancing the recruitment of CMKLR1 expressing immune cells [125].

In addition to enhancing the inflammatory response within adipose tissue, chemerin also enhances the inflammatory response of macrophages within tumors [126]. Limited evidence exists demonstrating increases in circulating chemerin concentration are associated with progression of cancers. Thus far the association between serum chemerin and gastric cell cancer is best characterized. Compared with healthy non-cancer subjects, stage 1
gastric cancer patients have higher serum concentration of chemerin [127]. In advanced stages of gastric cancer, high grade/aggressive cancer, serum chemerin concentration is higher than levels demonstrate in stage 1 [127]. In support of this others demonstrate that an elevation in pre-operative chemerin concentration is associated with poor post-operative prognosis and survival gastric cancer [128]. Chemerin promotes the progression of gastric cancer by increasing its invasiveness, the spread of cancer outside of the tissue the cancer has originated, but not proliferation [127]. Mechanisms for these increases in invasiveness include chemerin-induced increases in pro-invasive genes such as VEGF, MMP-7 and IL-6 and activation of MAPK signaling such as ERK1/2 and p38.

Omentin

Omentin was originally founded under the name “intelec- tin”. Under its first identity, this protein was isolated from small intestine paneth cells and classified as a soluble galactofuranose-binding lectin with a role in gut immunity against pathogenic bacteria [129]. In 2006, omentin-1, a 34 kDa protein, was determined to be secreted from adipose tissue in a depot-specific manner with higher expression and release from central (visceral) depots [130]. In humans, omentin is primarily expressed in adipose tissue stromal vascular cells and, as a secretory factor, acts as an endocrine factor to modulate systemic metabolism, but also acts locally in an autocrine and paracrine fashion [130]. The paracrine and endocrine effects of omentin in normal weight individuals function to enhance insulin sensitivity and glucose metabolism [130]. Omentin is also demonstrated to play a role in inflammatory responses and cell differentiation by AMPK/eNOS signaling pathway, which suppresses activation of JNK to suppress inflammation responses and increase cell differentiation [131]. Circulating omentin-1 levels in a healthy individual are reported to be roughly 0.37 μg/mL, but are significantly reduced in obese individuals to 0.31 μg/mL [132]. As stated previously, omentin levels are inversely correlated to obesity, but lower levels of omentin-1 are also found in patients with impaired glucose tolerance, type 2 diabetes, increased waist circumference, and elevated blood pressure [133]. Therefore, omentin-1 is considered to be predictive of metabolic abnormalities. In vitro studies have shown that omentin-1 treatment reverses these metabolic dysfunctions by stimulating glucose uptake via Akt activation [134]. Recently clinical research shows that cancers such as prostate [135], colon [136], liver [137], and colorectal [94] are associated with increases in omentin serum levels independent of various factors such as BMI, glucose, lipid parameters, disease differentiation [134, 136]. As demonstrated in HCC cells, omentin is considered anti-cancerous because it promotes apoptosis of cancer cells [137]. According to Zhang and Zhou, omentin-1 inhibits HCC proliferation via upregulating p21 protein in human HCC cells, which in turn increases p53 protein, a tumor suppressor gene [137]. Omentin-1 also promotes HCC apoptosis by increasing the bax-to-bacl-2 ratio and inducing capases-3 activation [137]. To the best of our knowledge, there are no additional studies directly associating the anti-inflammatory and tumor-suppressing effects of omentin on other cancers; therefore, this would be the most profitable step in the upcoming research of omentin.

Nesfatin

Derived from the protein nucleobindin 2, nesfatin-1 discovered in 2006, also known as NUCB2, is identified as an anorexigenic peptide that regulates appetite and body weight [138]. Originally, nesfatin-1/NUCB2 was discovered in hypothalamic nuclei but is now characterized to be expressed in numerous tissues such as the arcuate nuclei, lateral hypothalamus, paraventricular nuclei, supraoptic nuclei, stomach tissues, pancreatic islets, testis and adipose tissues [138, 139]. Nesfatin-1 secretion from adipose tissue, in particular subcutaneous adipose depots, is increased in obesity and by other factors such as pro-inflammatory cytokines such as TNF-α and IL-6 as well as insulin and dexamethasone [94, 138]. In obesity nesfatin-1 is suggested to play a role in the enhancement of lipid accumulation pathways [138].

To the best of our knowledge, there is currently only one prospective study that reports a connection between circulating nesfatin-1 concentration and cancer. In this study, nesfatin-1 levels are decreased in lung cancer patients with, but not without, cachexia; hence, nesfa- tin-1 levels are decreased with decrease adiposity [139]. Additional studies in cell lines, however, have further elucidated the effect of nesfatin-1 on cancer cell regulation. According to Xu et al. [140], nesfatin-1 treatment to the ovarian epithelial carcinoma cell line HO-8910 inhibits cancer cell proliferation by altering elements of the cell cycle, leading to a decrease in the number of cells that reach maturation. Nesfatin-1 treatment in this study is also reported to promote apoptosis of the HO-9010 cells via the mammalian target of rapamycin (mTOR) signaling
pathway [140]. mTOR, a central cell growth regulator that controls cell proliferation, had a significant decrease in activation with nesfatin-1 treatment, as did its downstream target, the S6 ribosomal protein [140]. In addition, the activity of caspase-3, a well-known apoptosis marker in mammalian cells, was increased, which further adds to the apoptosis effect [140]. Finally, in this study, RhoA/ROCK pathway ratios were measured to further solidify the findings that nesfatin-1 both promotes apoptosis of cancerous cells and inhibits their proliferation [13]. Many cellular processes, including apoptosis, are dependent on RhoA, a small GTPase, and its downstream effector, Rho-associated coiled coil-containing protein kinase (ROCK) [141]. Nesfatin-1 significantly increased RhoA activity levels, also increasing the activity of ROCK, thus inducing apoptosis and further inhibiting the proliferation of HO-9010 cells [140]. Ideally, further research on the benefits of nesfatin-1 treatment is in order on a number of various other cancers and after then, rodent specific studies to identify direct correlation.

Vaspin

Vaspin, a visceral adipose tissue-derived serine protease inhibitor known mainly for its insulin-sensitizing effects and modulatory role on glucose tolerance [134]. This 50 k-Da adipokine was first discovered when identifying genes that were differentially expressed between the development of obesity and type 2 diabetes in a rat model study; vaspin was identified to be increased in obesity [134]. Thereafter, increased vaspin levels have been reported to be linked to diabetes, metabolic syndrome, obesity, coronary artery disease and impaired insulin sensitivity [142].

There is only one recent study that has used a rodent model to directly correlate the effects of vaspin with obesity. According to Nakatuska and colleagues, vaspin transgenic (Tg) mice fed a high-fat-high sucrose (HFHS) diet were protected from increased adiposity, glucose intolerance, hepatic steatosis and obesity-induced inflammation [143]. Vaspin knockout mice, however, had opposite results with glucose intolerance, being highly associated with the upregulation of liver ER stress markers (marker of liver dysregulation) [143]. The effect of liver ER stress on insulin resistance/glucose intolerance in this model involved down regulation of ER chaperone proteins, such as 78 k-Da glucose-regulated protein (GRP78) [16]. Hence, increased expression of GRP78 in the liver is proposed to be metabolically beneficial. Indeed, in lean rodents, vaspin interacts with GRP78 to induce intracellular signaling that activates Akt and AMPK, which improves glucose and lipid metabolism and relieves metabolic dysfunction and inflammatory responses in obesity [144].

To the best of our knowledge, there are only two recent prospective studies relating the link between vaspin and specific cancers: one on colorectal [94] and another on endometrial [71]. Neither study has successfully identified the mechanism of vaspin to the respective cancer. Furthermore, the results from one study contradicts the other. There are reports of lower levels of vaspin in endometrial cancer results while there are reports of higher levels in colorectal [10, 18]. Clearly there is much more need research on the benefits and effects of vaspin on all levels from molecular to demographic.

Cytokines

Cytokines are another class of molecule that have been heavily indicated in the induction and pathogenesis of cancer. Cytokines are primarily linked to the development of cancers by way of their influence on inflammation, mainly chronic low grade inflammation associated with many diseases such as obesity, hence inflammation is one of the major factors that links obesity to the development of its associated co-morbidities [145]. One of the proposed major connections between cytokines and cancer is through the molecule NF-kB. NF-kB is a transcription factor that is activated in response to a number of stimuli, including inflammatory molecules (II-6, TNF-alpha, and II-1B), growth factors, viruses and bacteria. NF-kB in turn is linked to cell proliferation, apoptosis, angiogenesis and metastasis [146].

One of the major cytokines regulated through NF-kB and that has been heavily studied in its relationship to cancer is IL-6 [147]. Cytokines within the IL-6 family include, but are not limited to, IL-11, IL-27 and IL-31 [145]. This cytokine family has been investigated in relation to several cancers including colon and prostate [148]. It was demonstrated that in prostate cancers, IL-6 functionally changes from a growth inhibitor to a growth promoter with the ability to potentiate cancer cell growth [148]. It was also demonstrated in colon cancers IL-6 promotes tumor development and growth via Stat3 signaling especially in the early stages of development in relation to colitis [149].

The important aspect of cytokines in cancer development has been narrowed down to the role that they play in inflammation. Much of the inflammatory response...
has been demonstrated to flow through the transcription factor NF-kB that is activated by many of the inflammatory molecules and machinery [150]. One of the most important aspects that has been demonstrated for NF-kB is its ability to activate anti-apoptotic gene expression that blocks the apoptotic process that is induced by many of the inflammatory cytokines such as TNF-alpha [151]. Combining upregulation of inflammatory cytokines through tissue injury as well as increased adipokine secretion by adipose tissue and immune molecules, especially in a state of obesity, and the ability of many of these to induce NF-kB, overall promotes a protumorigenic environment.

**Conclusion**

Dissecting mechanisms underlying adipokine involvement in obesity-driven cancer is of high importance because of risk reduction and treatment to prevent recurrence. Current suggestions to decrease obesity-associated cancer risk include lifestyle interventions such as losing weight, physical activity and dietary modifications. The epidemiological, pathophysiology and mechanistic studies provided to date signify the important role adipokines play in cancer progression and reoccurrence. The previous studies clearly demonstrate that adipose cytokines play in cancer progression and recurrence. Current suggestions to decrease obesity-associated cancer risk by hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev 2008;17:73–9.


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