



Classic and Novel Adipocytokines at the Intersection of Obesity and Cancer: Diagnostic and Therapeutic Strategies

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Abstract

Purpose of Review In this review, we investigate the role of classic and novel adipocytokines in cancer pathogenesis synthesizing the mechanisms underlying the association between adipocytokines and malignancy. Special emphasis is given on novel adipocytokines as new evidence is emerging regarding their entanglement in neoplastic development.

Recent Findings Recent data have emphasized the role of the triad of overweight/obesity, insulin resistance and adipocytokines in cancer. In the setting of obesity, classic and novel adipocytokines present independent and joint effects on activation of major intracellular signaling pathways implicated in cell proliferation, expansion, survival, adhesion, invasion, and metastasis. Until now, more than 15 adipocytokines have been associated with cancer, and this list continues to expand. While the plethora of circulating pro-inflammatory adipocytokines, such as leptin, resistin, extracellular nicotinamide phosphoribosyl transferase, and chemerin are elevated in malignancies, some adipocytokines such as adiponectin and omentin-1 are generally decreased in cancers and are considered protective against carcinogenesis.

Summary Elucidating the intertwining of inflammation, cellular bioenergetics, and adiposopathy is significant for the development of preventive, diagnostic, and therapeutic strategies against cancer. Novel more effective and safe adipocytokine-centered therapeutic interventions may pave the way for targeted oncotherapy.

Keywords Adipocytokine · Adipokine · Adiponectin · Apelin · Cancer · Chemerin · Leptin · Nesfatin · Nicotinamide phosphoribosyltransferase · Obesity · Omentin · Oncostatin · Osteopontin · Resistin · Retinol-binding protein 4 · Vaspin · Visfatin

Abbreviations

AdipoR1/R2	Adiponectin receptor 1/2	BC	Breast cancer
Akt	v-Akt murine thymoma viral oncogene homolog	BMI	Body mass index
AMPK	5' AMP-activated protein kinase	CVD	Cardiovascular disease
		DM	Diabetes mellitus
		DNA	Deoxyribonucleic acid

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ER	Estrogen receptor
ERK 1/2	Extracellular signal-regulated kinase 1/2
GRP78	Glucose-regulated protein 78
GTP	Guanosine-5'-triphosphate
HIF-1a	Hypoxia-inducible factor-1a
IL	Interleukin
IGF	Insulin-like growth factor
IRS	Insulin receptor substrate
JAK	Janus kinase
JNK	Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
LEPR	Leptin receptor
LIFR α	Leukemia inhibitory receptor alpha
MMP	Matrix metalloproteinase
mTOR	Mammalian target of rapamycin
NAD	Nicotinamide adenine dinucleotide
Nampt	Nicotinamide phosphoribosyl transferase
NF- κ B	Nuclear factor- κ B
NSCLC	Non-small cell lung carcinoma
OSM	Oncostatin M
PBEF	Pre-B cell colony-enhancing factor
PCOS	Polycystic ovary syndrome
PI3K	Phosphatidylinositol 3-kinase
PPAR	Peroxisome proliferator-activated receptors
PR	Progesterone receptor
RBP-4	Retinol-binding protein
ROCK	Rho-associated coiled coil-containing protein kinase
SNPs	Single nucleotide polymorphisms
STAT	Signal transducer and activator of transcription
STRA6	Stimulated by retinoic acid 6
TLR	Toll-like receptor
TNF- α	Tumor necrosis factor- α
VCAM-1	Vascular cellular adhesion molecule-1
VEGF	Vascular endothelial growth factor
WHR	Waist-to-hip ratio

Introduction

Worldwide cancer constitutes the second leading cause of death [1]. It is expected that cancer incidence will continue to augment due to the increase in the prevalence of risk factors, mainly obesity and DM. In both developing and industrialized countries, there is a dramatic increase in the prevalence of overweight and obesity, defined as excessive or abnormal fat tissue accumulation and characterized as a BMI between 25 and 29.9 and over 30 kg/m² respectively [2]. Obesity is highly prevalent in females and in urban areas [3]. Generally, obesity develops when there is an imbalance between exceeding energy consumption from dietary intake and energy expenditure from physical and metabolic activity.

Obesity is associated with an increased risk of many chronic comorbidities associated with premature mortality, including DM type 2, hypertension, dyslipidemia, CVD, non-alcoholic fatty liver disease, and cancer [4].

There is sufficient evidence from prospective studies and meta-analyses that elevated body fatness, particularly visceral obesity, is associated with an increased risk for many malignancies including colorectal, postmenopausal breast, endometrial, gallbladder, thyroid, renal cell, ovarian, pancreatic, advanced prostate cancer, esophageal adenocarcinoma [5–8], and lymphohematopoietic cancer [9–13]. Emerging evidence associates higher body fatness in late adolescence and early adulthood with cancer risk at an older age [14]. The pathological expansion of white adipose tissue in obesity, also described as adiposopathy, is characterized by adipocyte hypertrophy and/or hyperplasia, hypoxia, oxidative stress response, disruption in the protein secretory pathway, and induction of angiogenesis [15]. Adiposopathy may provoke inflammatory, metabolic and immunologic changes affecting cell mutation rate, DNA repair, gene function, and induction of epigenetic changes permitting neoplastic transformation and growth [16•, 17•].

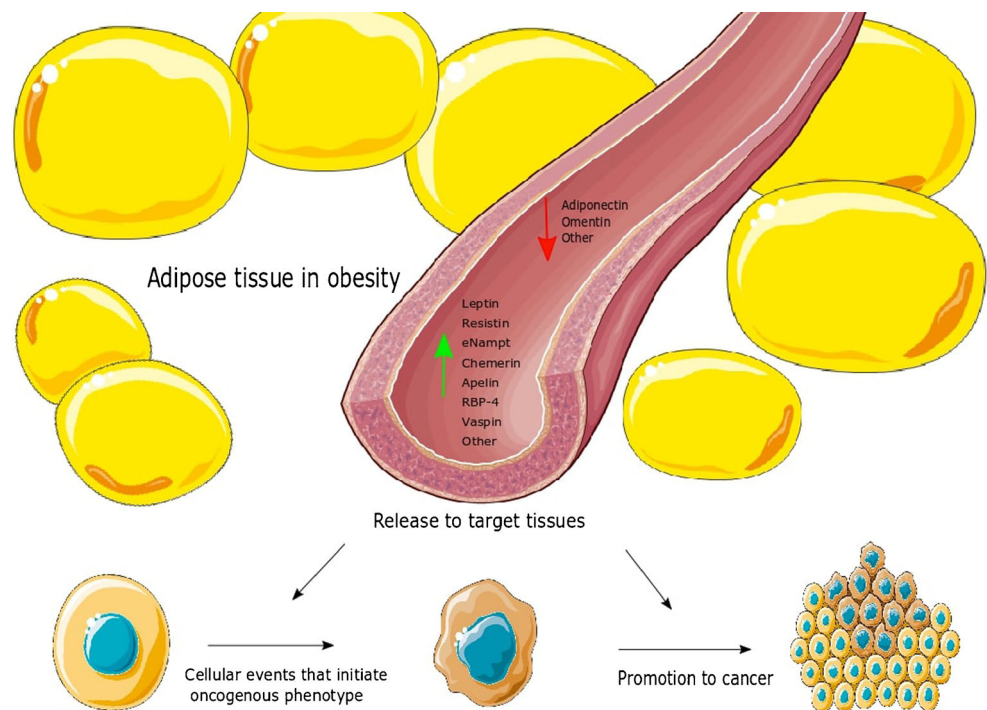
In the current review, we investigate the role of classic and novel adipocytokines in cancer pathogenesis synthesizing the mechanisms underlying the association between adipocytokines and malignancy. Special emphasis is given on novel adipocytokines as new evidence is emerging regarding their entanglement in neoplastic development. Elucidating the intertwining of inflammation, cellular bioenergetics, and adiposopathy is significant for the development of preventive, diagnostic, and therapeutic strategies against cancer.

Adipocytokines at the Intersection of Obesity and Cancer

Recent data have emphasized the role of the triad of overweight/obesity, insulin resistance and adipocytokines in cancer. Although the role of obesity in cancer pathogenesis is not fully elucidated, the main pathways connecting obesity and adiposopathy to malignancies comprise (i) hyperinsulinemia and insulin resistance; (ii) abnormalities of the IGF-I system; (iii) chronic low-grade systemic inflammation and oxidative stress; (iv) impaired immune function; (v) the impact of obesity/adiposopathy on sex hormones biosynthesis; and (vi) abnormal variations in the levels of adipocytokines (Fig. 1) [11, 17•, 18–21].

Besides its mere energy-storage properties, white adipose tissue is a dynamic endocrine organ secreting a constellation of functional heterogeneous adipocytokines, a group of polypeptides that regulate several physiologic and pathologic processes including insulin sensitivity, appetite, inflammation, innate and adaptive immunity, hematopoiesis, and angiogenesis [22, 23].

Fig. 1 Main variations of classic and novel adipocytokine serum concentrations in cancer



Until now, more than 15 adipocytokines have been associated with cancer, and this list is still expanding [24]. While the plethora of circulating pro-inflammatory adipocytokines, such as leptin, TNF- α , IL-6, resistin, and extracellular Nampt (eNampt) are elevated in malignancies, some adipocytokines such as adiponectin and omentin-1 are decreased in cancers and are considered protective against carcinogenesis [16••, 17••, 25–27]. Classic adipocytokines, formerly discovered adipocytokines such as leptin and adiponectin, have been sufficiently studied in cancer. A well-established connection of classic and novel adipocytokines with cancer risk and progression may include (1) altered plasma or serum concentrations in cancer patients; (2) their differential expression in malignant and benign tissues; (3) their upregulation in tumor tissues; (4) their correlation with advanced stage and poor prognosis as prognostic biomarkers; (5) their association with cancer therapy resistance as predictive biomarkers; (6) their association with *in vivo* and *in vitro* models of cancer; and (7) the association of genetic polymorphisms of adipocytokines genes with susceptibility to certain cancer types. Table 1 presents a summary of the mechanism of action of adipocytokines in cancer.

Classic Adipocytokines and Cancer

Adiponectin and Cancer

Adiponectin is a protein composed of 244 amino acids belonging to the C1q/TNF family of proteins [17••]. It was discovered almost simultaneously by four different research

groups, in mid-1990s [17••]. Adiponectin is secreted into circulation mainly by adipocytes [28]. Several receptors have been identified as binding sites for adiponectin: AdipoR1 (mainly expressed in skeletal muscles and endothelial cells), AdipoR2 (mainly expressed in liver), and T-cadherin [29, 30]. Adiponectin receptors are expressed in almost any tissue as well as in cancer cells [17••, 28]. Several growth factors such as platelet-derived growth factor, basic fibroblast growth factor, and heparin-binding epidermal growth factor-like growth factor are also bound by adiponectin [31].

A plethora of physiologic effects are exerted by adiponectin [32]. Adiponectin increases sensitivity to insulin and has anti-inflammatory and anti-atherogenic properties [32–34]. It also acts as cardioprotectant being involved in lipid metabolism [32–34]. Serum adiponectin levels correlate with various disease states [17]. Hypoadiponectinemia, which is the result of both genetic and/or environmental factors, is associated with insulin resistance, DM type 2, gestational DM, hypertension, metabolic syndrome, CVD, liver disease, and several malignancies [33–42]. On the other hand, increased adiponectin levels have been associated with anorexia nervosa, rheumatoid arthritis, and increased amount of proteinuria in chronic kidney disease [43–46]. In addition, there is evidence that high adiponectin levels are also associated with low risk for CVD in men, better glucose and lipid control in women [47–49], and lower risk for DM type 2 [50].

Besides its other properties, adiponectin exhibits anti-proliferative, anti-migratory, and pro-apoptotic actions [24, 51•]. Recombinant adiponectin has demonstrated anti-tumor effect when used in forms of leukemia, breast

Table 1 Summary of the mechanism of action of adipocytokines in cancer

Adipocytokine category	Adipocytokine name	Physiologic properties	Effects on oncogenesis	Signaling/mechanism of action
Classic	Adiponectin	↑ insulin sensitivity, lipid metabolism regulation, anti-inflammatory, anti-atherogenic	Anti-proliferative, anti-migratory, pro-apoptotic, ↓ bioavailability of several growth factors	AMPK, mTOR, NF-κB, JNK, STAT3
	Leptin	Central actions: Counteracts ghrelin and ↑ satiety, ↑ GH and thyroid hormones, ↑ (IGF)-1 binding capacity, LH pulsatility and sex steroid levels regulation, onset of puberty regulation Peripheral actions: ↑ basal O ₂ consumption in fat tissue, ↓ lipid accumulation in non-adipose tissues, ↑ glucose uptake and oxidation, glycogen synthesis, and lactate formation in skeletal muscle tissue, ↓ triacylglycerol in muscle, ↓ hepatic gluconeogenesis, ↓ glucose, galactose, and an absorption in small intestine, ↑ fructose and butyrate absorption in small intestine ↑ insulin resistance, pro-inflammatory	Anti-apoptotic, ↑ pro-inflammatory, ↑ angiogenesis	JAK/STAT3, MAPK, PI3K/Akt, ERK1/2, AMPK pathways, and IRS activation
Novel	Resistin	Cell metabolism, growth, inflammation	↑ cell proliferation, migration, and adhesion	MAPK, PI3K, NF-κB pathways
	eNamt/visfatin	Role in immunity, adipogenesis, and adipocyte metabolism	Pro-inflammatory, proliferative, anti-apoptotic, immunosuppressive, pro-angiogenic	MAPK, ERK 1/2, NF-κB, STAT3, PI3K-Akt
	Chemerin	Modulation of insulin effect	Inflammation, angiogenesis, induction of matrix metalloproteinases	MAPK, ERK pathways
	Omentin-1	Blood pressure control, insulin and histamine release regulation, angiogenesis, and hypothalamic regulation of fluid and food intake	Unclear	Akt, AMPK pathways
	Apelin	Vitamin A carrier, alters insulin sensitivity	Mitogenic, promotes cell survival, migration, and angiogenesis	ERK, PI3K/Akt pathways
	Retinol-binding protein 4	↑ insulin sensitivity, anti-inflammatory	Cell migration and proliferation	JAK/STAT, RhoA/Rock1, ERK pathways
	Vaspin	Anorexigenic, control of appetite and body weight	Anti-inflammatory, pro-apoptotic	Akt, AMPK pathways
	Nesfatin	Biominerzalization, inflammation, bone remodeling	↓ cell proliferation, ↑ cell apoptosis	RhoA/Rock1, mTOR pathways
	Osteopontin	Inflammatory response	↑ angiogenesis, metastasis, anti-apoptotic	Activation of MMP-2 and MMP-9
	Oncostatin M		Cell invasion, angiogenesis	JAK/STAT3, MAPK, PI3K pathways

adenocarcinoma, and fibrosarcoma [52]. In addition to its direct anti-tumor effect on cells, adiponectin results in lower bioavailability of various growth factors [31]. On the other hand, hypoadiponectinemia correlates with carcinogenesis, both directly and indirectly [17, 53]. Specifically, low adiponectin levels promote fatty acid and protein synthesis and, thus, cell growth, proliferation, and DNA mutagenesis [54]. Furthermore, hypoadiponectinemia supports tumor proliferation via the increase of anabolic hormones (insulin and IGF-1) and pro-inflammatory cytokines (TNF- α , IL-6) [54]. Recent meta-analyses have shown that decreased serum adiponectin levels are associated with cancers such as breast, prostate, endometrial, colorectal, tongue gastroesophageal, and also multiple myeloma and acute leukemias [55, 56]. In colorectal, gastric, and prostate cancer, low adiponectin levels are associated with cancer grade and stage. Interestingly, hypoadiponectinemia may serve as a useful biomarker for early cancer detection and prognosis [57, 58]. The combination of high BMI and hypoadiponectinemia is associated with more than sixfold the risk for endometrial cancer [59–61]. Regarding breast cancer, there is evidence that hypoadiponectinemia is an independent risk factor for disease regardless of age, menopause status, lymph nodes metastases, and hormone receptor status [62]. Adiponectin levels may also give information about the invasiveness of breast cancer [63]. The recent discovery of a novel adiponectin receptor 1 agonist as a therapeutic approach for DM may open analogous therapeutic avenues for anti-cancer treatment [64]. With a deeper understanding of the role of adiponectin in oncogenesis, safe drugs that modulate its downstream cellular pathways may emerge as an important therapeutic strategy in oncology.

Leptin and Cancer

Leptin, a hormone produced mainly from the adipose tissue, was discovered by Friedman and colleagues in 1994 [65]. Leptin secretion is proportionate to the adipose tissue mass and serves as a message of satiety and energy adequacy inhibiting appetite [66]. Leptin exerts its effects through the LEPR, which is a single transmembrane protein, expressed in most tissues. In turn, the receptor affects multiple intracellular signaling pathways including JAK/STAT3, MAPK, PI3K/Akt, ERK1/2, AMPK, and IRS pathways [66, 67]. In the context of cancer, JAK2 activates STAT3 and 5 that up-regulate the transcription of genes crucial to mechanisms of oncogenesis, such as cell proliferation, invasion, angiogenesis, and inflammation [28]. Furthermore, leptin increases the expression of anti-apoptotic proteins, inflammatory markers (TNF- α , IL-6), angiogenic factors (VEGF), and the HIF-1 α [68, 69]. The ERK phosphorylation results in downstream

activation of transcription factors that activate response elements of the *c-fos* gene promoting cell division [70]. Also, following JAK2 activation, PI3K and Akt are phosphorylated, and, as a result, glucose utilization, cell growth, cell proliferation, and apoptosis are induced [71]. Leptin has been shown to correlate with breast cancer depending on the menopausal status, showing a positive and negative correlation in postmenopausal and premenopausal women, respectively [72, 73]. The underlying oncogenic mechanism in mammary tissue involves mainly the JAK/STAT3 and PI3K pathways [74]. Moreover, leptin can inhibit apoptosis of BC cells favoring the expression of anti-apoptotic genes (*bcl-xL*, *bak*, and *bax*) and induce angiogenesis by stimulation of VEGF production [75]. Leptin displays an interesting interplay with ERs. Leptin can lead to stimulation of ER α , enhancement of aromatase expression, and suppression of p53 in ER-positive cancer cell lines [76, 77]. In the opposite direction, estradiol enhances the expression of leptin and LEPR in MCF7 BC cell lines [74]. The role of leptin on ER negative BC is not clear. In prostate cancer, leptin has been shown to promote oncogenicity in androgen insensitive prostate cancer cell lines [28] but not in androgen sensitive cell lines [78]. This is in accordance with hyperleptinemia observed in advanced prostate cancer which is more androgen refractory [67]. Also, leptin may promote oncogenesis in the gastrointestinal tract [67]. This has been shown in experimental settings in colon and gastric cancer. In patients with gastric cancer, leptin promoted invasiveness through the Rho/ROCK pathway [79] and correlated with aggressiveness of colorectal cancer [80].

However, in contrast to many *in vitro* studies where supraphysiologic levels of leptin were used, observational epidemiological studies have reported inconsistent associations between serum leptin levels and risk of several malignancies [26, 27, 81, 82]. Moreover, any associations of leptin with cancers reported in these studies may be due to the uncontrolled confounding via fat mass since all epidemiologic studies adjust for BMI which does not fully account for fat mass as a surrogate marker. Meta-analyses have shown positive associations of leptinemia with breast cancer, especially in overweight and obese women, a higher risk for endometrial cancer and inconclusive results for lung cancer [83, 84, 85]. Our research group, which has studied extensively adipocytokines in malignancies, has shown that hypoleptinemia and not hyperleptinemia was associated to pancreatic cancer independently from BMI and weight loss [86, 87], to B cell chronic lymphocytic leukemia [88] and to low-risk myelodysplastic syndrome after adjustment for BMI and other risk factors [89–91]. Therefore, although basic research studies have shown positive effects of leptin on cancer cells using higher doses of leptin levels, this may not have relevance to humans and cannot be translated into clinical applicability. Overall, the evidence has shown that leptin in normal physiological circulating levels is not associated with cancer risk.

Novel Adipocytokines and Cancer

Resistin and Cancer

Resistin is a small adipocytokine of 12.5 kDa, secreted by mononuclear inflammatory cells and adipose cells [25]. It was discovered in 2001 and was considered to be a linking hormone between obesity and diabetes (the name “resistin” implies resistance to insulin) [92]. Resistin binds TLR4 resulting in activation of the PI3K, p38 MAPK, and NF- κ B pathways [26]. The main effect of TLR4 binding is the secretion of pro-inflammatory cytokines such as TNF- α and IL-12 [26]. Additional effects include increased cell proliferation, migration, and adhesion [25].

The most notable physiological effects of resistin include potential pro-diabetic and pro-inflammatory activity [25]. There is evidence that hyperresistinemia is associated with many disease states comprising visceral obesity, coronary artery disease, lung disease, various malignancies, and critical illness [25, 93, 94]. Resistin may trigger tumorigenesis via inflammation (PI3K and NF- κ B pathways), immune cell extravasation (MAPK pathway), expression of cardinal molecules for adhesion of cancerous cells (NF- κ B pathway), and promotion of survival and invasiveness of tumor cells (PI3K and MAPK pathways) [24].

In a recent meta-analysis, hyperresistinemia was linked to an increased incidence of obesity-related cancers such as breast, endometrial, and colorectal cancer [95]. Some epidemiological studies, mainly case-control studies, have also linked high resistin levels to non-obesity-related cancers (such as esophageal, gastric and lung cancer) [25]. Additionally, increased resistin levels have been associated with lymphohematopoietic cancer [25]. However, despite its strong association to various types of cancers, resistin presents a limited diagnostic or predictive ability as a cancer biomarker [95].

Visfatin/eNampt and Cancer

Visfatin, also known as Nampt or PBEF, is a 52-kDa protein, the product of the NAMPT gene, that acts as an enzyme, adipocytokine, and a growth factor [96–98]. Nampt can be found in two forms, the intracellular-iNampt, and the extracellular-eNampt [16••]. iNampt participates in NAD biosynthesis, an important electron carrier, representing thereby a crucial function in cell metabolism. eNampt is excreted by a variety of tissues such as adipose, liver, and heart, and the mechanism that this is accomplished is thought to be cell lysis [97]. eNampt has been associated with various pathologies including diabetes, obesity, aging, atherosclerosis, cardiac hypertrophy, and autoimmune diseases [99–101]. Regarding oncogenesis, eNampt displays pro-inflammatory, proliferative, anti-apoptotic, and pro-angiogenic effects [102]. It induces

inflammation through the activation of NF- κ B and promotes proliferation through the upregulation of Notch-1, cyclin D1, cyclin dependent kinase 2, MAPKs, ERK-1/2, and p38 signaling pathways [7, 103–105]. Moreover, eNampt may function as an endocrine mediator in some cancers and can contribute through its immunosuppressive properties to the characteristic immune-evasive properties of malignancies [106]. Serum eNampt is elevated in many cancers and is generally correlated with worse prognosis and advanced stage [102, 107]. Specifically, it has been associated not only with the risk of obesity-associated malignancies, such as breast, endometrial, and colorectal cancer [16••] but also with the risk of male oral squamous cell, gastric and hepatocellular carcinoma, bladder and prostate cancer, non-small cell lung cancer, brain tumors, and hematologic malignancies [16••, 24]. Molecules that inhibit Nampt are being investigated in clinical trials, either as a monotherapy or as a part of combination therapy that enhances chemotherapy effects by triggering depletion of energy in cancer cells [16••].

Chemerin and Cancer

Chemerin is a small protein of 16 kDa, expressed in lung, liver, and white adipose tissue [108]. It is involved in innate and adaptive immunity by binding protein-coupled receptor chemokine-like receptor 1 (CMLR1) [109]. Apart from immunity, chemerin plays a role in adipogenesis and adipocyte metabolism [108, 110].

Chemerin levels are positively correlated with BMI and components of the metabolic syndrome [24, 111, 112]. Increased chemerin levels have been associated with neuroblastoma, NSCLC, and tongue, esophageal, gastric, and colorectal cancer [113, 114]. Interestingly, chemerin levels may serve as an important prognostic factor for gastric cancer patients' post-operative survival [115]. The mechanisms by which chemerin is promoting tumorigenesis comprise inflammation, angiogenesis, and induction of matrix metalloproteinases [24, 116]. It has recently been suggested that the chemerin/CMLR1 pathway may also serve as a potential therapeutic target for malignancies such as neuroblastoma [117].

On the contrary, a recent study in mice hepatocellular cancer (HCC) showed that chemerin may have tumor-inhibitory effects, by suppressing the inflammatory microenvironment of the tumor [118•]. This fact may underscore a potential therapeutic role of chemerin against inflammation-associated tumors such as HCC [118•]. It also implies that chemerin may present differential effects on different types of cancers.

Omentin-1 and Cancer

Omentin-1, discovered in 2006 and originally recognized as intelectin-1, is secreted from the adipose tissue, mainly from the visceral fat [119]. It has been considered as one of the

missing links explaining the higher burden of DM type 2 and cardiovascular disease attributed to visceral obesity compared to subcutaneous obesity [67]. Omentin-1 is produced by stromal vascular cells of the adipose tissue exerting its actions in an endocrine, autocrine, and paracrine manner [119]. Omentin-1 enhances insulin's effects by stimulating insulin-mediated glucose uptake by subcutaneous and visceral adipocytes *in vitro* via the Akt signaling [119]. Besides the inverse correlation of omentin-1 levels with obesity, its levels are decreased under the spectrum of altered metabolic parameters including increased waist circumference, dyslipidemia, and hypertension [120]. As a result, omentin-1 may function as a marker of cardiovascular risk [121]. In HEPG2 cell lines, omentin-1 exerted anti-oncogenic effects through promotion of apoptosis via upregulating p21 that, in turn, increased p53, bax/bcl2 ratio and activated caspase 3 system [122]. Elevated levels of omentin-1 were detected in patients with malignant mesothelioma and prostate cancer [123]. On the contrary, omentin-1 was markedly decreased in renal cancer patients [124]. Omentin-1 was associated with better outcomes in patients with gastric and stage IV colorectal cancer [123]. Baseline omentin-1 levels have been correlated with colorectal cancer risk, presenting a potential interaction with the adiposity state of the patients [125]. This contradictory finding to the tumor suppressive properties of omentin-1 was attributed to its potential correlation with intestinal inflammation and the enhancement of the Akt pathway [125]. Furthermore, omentin-1 was elevated in stage III colorectal cancer patients in comparison to healthy controls [126]. Pancreatic cancer patients displayed higher levels of omentin-1 as a compensatory response to the inflammation and/or weight loss due to cancer cachexia, a complex metabolic state characterized by loss of muscle and adipose tissue [127]. Omentin-1 correlated with pancreatic tumor size but failed to predict survival [127]. Finally, omentin-1 effectively inhibited the growth, invasion, and metastasis of neuroblastoma cells *in vitro* and *in vivo* via stimulation of the N-myc downstream-regulated gene 2 expression [128].

Apelin and Cancer

Apelin is a 9-kDa peptide identified in 1998. It is expressed in various different tissues such as the brain, liver, kidney, heart, lung, gastrointestinal tract, adrenal gland, adipose tissue, and endothelium [24, 129]. Apelin binds a G protein-coupled receptor which results in the activation of the ERK and PI3K/Akt pathways [129].

The physiologic functions of apelin include blood pressure control, insulin and histamine release regulation, angiogenesis, and hypothalamic regulation of fluid and food intake [130]. There is no clear association between BMI and circulating apelin levels [131] while there is a strong correlation of

this adipocytokine with hyperinsulinemia and pathogenesis of DM type 2 [132].

Higher apelin levels have been associated with cholangiocarcinoma, prostate, oral, ovarian, colon, endometrial, lung, and gastroesophageal cancers [133], serving as a potential marker for cancer progression [134]. Apelin may promote metastasis through enhanced proliferation, migration, invasion, and resistance to apoptosis [133].

Retinol-Binding Protein 4 and Cancer

Retinol-binding protein 4 (RBP4), a soluble 21-kDa polypeptide, is mainly produced by the liver [135]. It functions as a vitamin A carrier that transports it to the periphery, throughout the body [136]. Adipose tissue is a secondary site of RBP4 synthesis; hence, RBP4 is classified as an adipocytokine. When it reaches its target tissues, RBP4 possibly acts by binding to cell surface receptors or through retinoic acid and retinoic acid-X receptors [136]. Although RBP-4 has been implicated in insulin resistance, epidemiological evidence has not been conclusive [137, 138]. RBP4 has been positively associated with triglycerides, total cholesterol, LDL-cholesterol, and high blood pressure [135]. Regarding oncogenesis, RBP4 promotes JAK/STAT signaling via its receptor STRA6. In culture with RBP-4, breast and colon carcinoma cells as well as fibroblasts acquired oncogenic properties such as cell proliferation, migration, and invasion [135]. However, proliferation of colon tumor cells was significantly inhibited after knocking down STRA6 receptor [135]. Upregulation of STRA6 and RBP4 has been documented in colorectal and breast cancer [135]. In ovarian cancer cell lines, RBP4 stimulated cancer cell migration and proliferation through the RhoA/Rock1 and ERK pathways, suggesting a potential oncogenic role [139]. Observational studies associating RBP4 and cancer have been inconclusive. In a case-control study, elevated RBP4 levels were found in BC patients, especially those who were PR and ER receptor negative [140]. On the contrary, in a cross-sectional study, lower RBP4 levels were found in patients with CRC [141].

Vaspin and Cancer

Vaspin was first identified in the Otsuka Long-Evans Tokushima fatty rat and is a protease inhibitor [24, 142]. It is mainly secreted by visceral adipose tissue [24]. Other sites of production are the stomach, liver, pancreas, and hypothalamus [24].

Despite its unclear mechanism of action, vaspin binds GRP78 and activates Akt and AMPK which regulate glucose and lipid metabolism [24]. Through these pathways, vaspin may improve obesity-related metabolism dysfunction [24]. Vaspin increases insulin sensitivity and presents anti-inflammatory and apoptotic properties [142, 143]. Vaspin

may play a role in various diseases such as diabetes, obesity, metabolic syndrome, PCOS, and coronary artery disease [144, 145]. The potential connection of vaspin with cancer needs further investigation [22]. From observational studies, it has been shown that decreased vaspin levels are associated with endometrial cancer, while increased levels are associated with CRC [146, 147]. In a recent study, it is suggested that vaspin, like leptin, may be a helpful assessment tool for the clinical staging of endometrial cancer [148].

Nesfatin and Cancer

Nesfatin-1, discovered in 2006, was identified as an anorexigenic peptide with a role in appetite control and body weight [149, 150]. It is the N-terminal part of nucleobindin 2 (NUCB2) and is expressed in brain loci pertaining to feeding regulation [149]. Besides its brain expression, nesfatin-1 is mainly produced by the subcutaneous adipose tissue but also the gastric endocrine cells and the pancreatic beta cells [151]. Cytokines that promote inflammation, such as TNF- α and IL-6, induce the secretion of nesfatin [24]. As per its oncogenicity, nesfatin inhibited cell proliferation by altering elements of the cell cycle in HO-8910 ovarian epithelial carcinoma cells, an effect reversed by the RhoA/ROCK signaling pathway [152]. Among other mechanisms, apoptosis is dependent on the GTPase RhoA and its downstream effector, ROCK, a further downstream molecule [153]. Nesfatin-1 increased RhoA activity, as well as the activity of ROCK, thus triggering apoptosis of HO-9010 cells [152]. Moreover, nesfatin-1 induced apoptosis in HO-9010 cells by modulating the mTOR pathway [152]. Serum nesfatin has been found significantly lower in lung cancer patients, mainly attributed to cachexia [154].

Osteopontin and Cancer

Osteopontin is a pro-inflammatory adipocytokine that was first described as a protein of bone calcified matrix [155]. It is expressed in a plethora of different cell types such as adipocytes, immune system cells, hepatocytes, smooth and skeletal muscle cells, endothelial cells, osteoblasts, osteocytes, chondrocytes, and fibroblasts [148]. It is also found in tissues such as the brain, placenta, mammary glands, and kidneys [156]. It induces the activation of MMP-2 and MMP-9 [157, 158]. Osteopontin is involved in biomineralization, inflammation and remodeling [156]. It is linked to disease states such as obesity, DM, non-alcoholic steatohepatitis, and cancer [156, 159]. An overexpression of osteopontin is present in various types of cancer, such as stomach, lung, breast, and ovarian cancer and melanoma [158, 160]. Osteopontin may be used as a biomarker characterizing cancer aggression, especially grade [161]. The mechanisms connecting osteopontin with tumorigenesis include angiogenesis, metastasis, and evasion of apoptosis [159, 162]. Several strategies such as blocking

osteopontin activity with antibodies/small molecule inhibitors and osteopontin silencing via the use of RNAi technology, are suggested as therapeutic approaches in cancer [161]. However, further investigation on these novel targeted therapies is needed [161].

Oncostatin and Cancer

Oncostatin M (OSM) was discovered in 1986, as a molecule that can effectively inhibit the proliferation of melanoma cell lines as well as other cancer cell lines, exhibiting oncogenic properties [163]. OSM belongs to the IL-6 family being secreted by activated T cells and macrophages and involved in the inflammatory response [164]. OSM interacts with the cell signaling molecule gp130, requiring a second receptor to join the complex for the signal to be transduced [165]. It binds to the gp130 complex with either LIFR α , termed as OSM receptor type I, or OSMR β complex termed as the OSM receptor type II [165]. Several signaling pathways including JAK/STAT3, MAPK, and PI3K can be stimulated by gp130 cytokines, although their spectrum depends on the target tissue [165]. OSM stimulates growth of Kaposi sarcoma cells through the ERK-2 and PI3K pathways [166, 167]. Recent evidence has shown that the adipose tissue can secrete OSM promoting BC progression through JAK/STAT3 pathway up-regulation [168]. Moreover, OSM may promote cell invasion and angiogenesis in osteosarcoma cell lines facilitating matrix degradation and angiogenesis in prostate cancer cells [169, 170]. In a mouse breast cancer model, OSM promoted metastasis, increased circulating tumor cells, and decreased survival [171]. Oncostatin levels have been associated with a poor outcome in breast cancer patients, an effect possibly mediated by estrogen receptor downregulation [172].

Preventive and Clinical Implications

Based on current epidemiological evidence, a considerable percentage of cancer cases may be preventable through maintaining a healthy weight, following a diet with fruits, vegetables, and olive oil, increasing physical exercise and reducing alcohol intake [173]. The American Society of Clinical Oncology has underscored that obesity is one of the most important preventable lifestyle risk factor for cancer mortality [174], overtaking smoking.

Besides expansion of fat mass, obesity is considered a systemic endocrine dysfunction characterized by chronic inflammation. Adipocytes support tumor metabolism while their products, adipocytokines, are cardinal mediators of tumor progression via their paracrine and endocrine actions. In the setting of obesity, classic and novel adipocytokines present independent and joint effects on activation of major intracellular

signaling pathways implicated in cell proliferation, expansion, survival, adhesion, invasion, and metastasis.

Plasma levels of classic (adiponectin and leptin) and novel adipocytokines such as resistin, eNamt, and chemerin may be modifiable by weight control, adoption of a balanced diet, and physical activity [16•, 25, 175, 176]. Bariatric surgery is linked to cancer risk reduction through modulation of the adipocytokines profile, particularly elevation of adiponectin and decrease of leptin, resistin, eNamt, and chemerin [177–180]. Paradoxically, although novel adipocytokines are not only adipose-cell-derived, they are responsive to adiposity alterations. Glycemic control can restore adipocytokine concentrations [181]. Pharmacologic agents such as metformin or PPAR- γ agonists that increase adiponectin and decrease resistin and eNamt levels in both humans and mice could be at the forefront of therapeutic strategies for obesity-related malignancies [16•, 25, 181, 182]. Lipid-lowering drugs, calcium-channel blockers, folic acid, oleic acid, and vitamin C and D supplementation may significantly improve adipocytokine levels [4, 16•, 25]. Some nutraceuticals such as curcumin, a polyphenol derived from turmeric, may modulate mRNA and protein levels of resistin and eNamt [183].

In preclinical studies, pegylated leptin receptor antagonist 2 has been shown to decrease the proliferation and angiogenesis of BC cells [184, 185]. Peptide-based adiponectin receptor agonists such as ADP355, which is an adiponectin mimetic, has been reported to limit the proliferation of adiponectin receptor-positive cancer cell lines [186, 187]. Targeting resistin and eNamt inhibition, either by biochemical or antibody neutralization, by antisense oligonucleotides, or by antagonism of their putative receptors, may be an effective strategy in cancer therapeutics, particularly in depleting the tumor inflammatory microenvironment [16•, 25]. If their receptors and signaling pathways are clearly determined, inhibition of resistin and eNamt downstream targets may be further explored in the cancer therapeutics armamentarium. Combination treatment with Namt inhibitors and chemotherapeutic drugs or radiation may represent an emerging strategy enhancing the efficacy of existing chemotherapeutic agents [16•]. Hence, continued research is necessary to establish whether novel adipocytokines could be a potential therapeutic target for both cancer and obesity.

Adipocytokines, particularly adiponectin, are potentially useful diagnostic and prognostic biomarkers, reflecting advanced stage, adverse prognosis, and inflammatory state. Hypoadiponectinemia warrants assiduous investigation to rule out cardiometabolic diseases and cancer [188, 189] as well as worsened prognosis in cancer [182]. Recent data suggest that eNamt and resistin may be promising cancer biomarkers reflecting advanced stage and adverse prognosis [16•, 25, 190, 191]. Nevertheless, more large-scale prospective and longitudinal studies are needed to explore the diagnostic, prognostic, and predictive utility of classic and novel

adipocytokines as cancer biomarkers and to rule out a potential “epiphenomenon” effect of adipocytokines variation in the context of tumor systemic inflammatory response.

The development of reliable, “user friendly” and practical automated laboratory techniques (enzyme-linked immunosorbent, electro-chemiluminescence immunoassays, etc.) and standardization of immunoassay procedures are needed to investigate the physiologic and pathophysiological relevance of adipocytokines. Also, there is a considerable number of unanswered practical issues in the clinical laboratory setting. What adipocytokine levels should be considered unhealthy and what are their optimal concentrations for cancer prevention? Their reference range should be determined as they may differ by age, gender, race, various preanalytical parameters, and assay methodology. Detection of SNPs of adipocytokines genes and quantification of adipocytokine expression in neoplastic tissues by using molecular techniques could provide additional data for prognosis and therapeutic response [17•, 192, 193]. To investigate the potential association of adipocytokines and cancer risk, adequately powered Mendelian randomization studies employing genetic determinants of adipocytokines derived from genome-wide associations studies are ideal because they circumvent confounding of lifestyle variables and reverse causation [194–196].

Conclusion

In conclusion, this review provides evidence for a connection between classic and novel adipocytokines, and cancer. High-throughput technologies such as proteomics and metabolomics will identify novel adipocytokines. Further research in basic and translational research is essential to elucidate the ontological role of novel adipocytokines and their interplay in cancer pathogenesis. Basic research studies are required to investigate the epigenetic regulation of adipocytokines genes and to map out their receptors and critical signaling pathways. More clinical longitudinal studies are expected to determine a wide spectrum of obesity-related biomarkers and assess their clinical utility in cancer prognosis and follow-up. Finally, novel more effective and safe adipocytokine-centered therapeutic interventions may pave the way for targeted oncotherapy.

Compliance with Ethical Standards

Conflict of Interest Nikolaos Spyrou, Konstantinos I. Avgerinos, Christos S Mantzoros, and Maria Dalamaga declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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