Obesity and Cancer: Linked Molecular Mechanisms

28

Erika Di Zazzo, Monica Rienzo, Maria Michela Marino, Donatella Fiore, Chiara Piscopo, Amelia Casamassimi, Bruno Moncharmont, and Ciro Abbondanza

Contents

Introduction 386

Comorbidities 386
Biological Mechanisms Linking Obesity to Cancer 386
Hyperinsulinemia/Insulin Resistance 388

Sex Hormones 388
Adipokines and Cancer 388
Adiponectin and Cancer 389

Hypoadiponectinemia 389
Breast Cancer 389
Gastrointestinal Malignancies 389
Colorectal Cancer 390
Ovarian Cancer 390
Endometrial Cancer 390
Prostate Cancer 391

Low Chronic Inflammation 391

The Obesity Paradox in Cancer 391

Obesity and Therapy 392
Drug Dosage 392

Specific Cancer Therapies for Obese and Diabetic Patients? 392
Metformin 392

E. Di Zazzo (✉) · B. Moncharmont
Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso, Italy
e-mail: erika.dizazzo@unimol.it

M. Rienzo · M. M. Marino · A. Casamassimi · C. Abbondanza
Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy

D. Fiore · C. Piscopo
Department of Pharmacy, University of Salerno, Fisciano, (SA), Italy

J. Faintuch and S. Faintuch (eds.), *Obesity and Diabetes*, https://doi.org/10.1007/978-3-030-53370-0_28

Thiazolidinediones (TZDs) and Other Agents 393
Therapies Targeting APN 393
Oral Adiponectin Receptor Agonist 393
Statins and Assorted Drugs 393
References 394

Abstract

Obesity is related to metabolic defects that may promote not only cancer initiation, but also its progression. The molecular basis for the association between obesity and cancer is not fully understood; however, many pathways are being investigated including hyperinsulinemia/insulin resistance (IR) and abnormalities of the insulin-like growth factor-1 (IGF-1) signaling, sex hormones biosynthesis and pathway, alterations in adipokines pathophysiology, and subclinical chronic low-grade inflammation. In this chapter, we analyze the current knowledge on the proposed biological mechanisms, especially focusing on the role of adiponectin (APN).

Keywords

Obesity · Cancer · Insulin-like growth factor-1 signaling · Sex hormones · adipokines · adiponectin · Low-grade inflammation

Introduction

White adipose tissue (WAT) was formerly studied in connection with caloric reserves, mechanic and thermal insulation, and sexual attraction. However, it is unquestionably a complex endocrine organ (Coelho et al. 2013). Adipocytes constitute 90% of the cells, whereas the stromal-vascular components include endothelial cells (10–20% of cells), pericytes (3–5%), fibroblasts, and others (15–30%). Stem and progenitor cells (0.1%) should not be neglected, along with T- and B-lymphocytes, macrophages, dendritic cells, and others (Cozzo et al. 2017). Sex steroid hormones, insulin resistance, growth factors, cytokines, and adipokines are all influenced by this cellular environment (Osborn and Olefsky 2012). Many cancer types are impacted by the same molecules and pathways (Sung et al. 2019).

Excessive body weight promotes elevated free fatty acids (FFA), triglycerides, glucose, insulin resistance, and insulin production, some of which could also stimulate cancer progression (Osborn and Olefsky 2012).

Comorbidities

Obesity predisposes to metabolic, cardiovascular diseases, as well as of several malignancies (Sung et al. 2019; Global BMI Mortality Collaboration et al. 2016; Goodwin and Stambolic 2015; GBD 2015 Obesity Collaborators et al. 2017), a phenomenon called as "adiponcosis" (Bifulco and Ciaglia 2017).

Cancers of digestive organs, like colon cancer, and tissues with endocrine links, such as breast, ovarian, endometrial, and prostate cancers, receive most attention (Sung et al. 2019; Kyrgiou et al. 2017; Tumminia et al. 2019). Cancer is the number two most fatal human condition, after cardiovascular disease, whereas obesity and related aberrations could be aggravating oncological mechanisms (Sung et al. 2019; Goodwin and Stambolic 2015).

Biological Mechanisms Linking Obesity to Cancer

Possible biological mechanisms comprise hyperinsulinemia/insulin resistance (IR) and abnormalities of the insulin-like growth factor-1 (IGF-1) signaling, sex hormones biosynthesis and

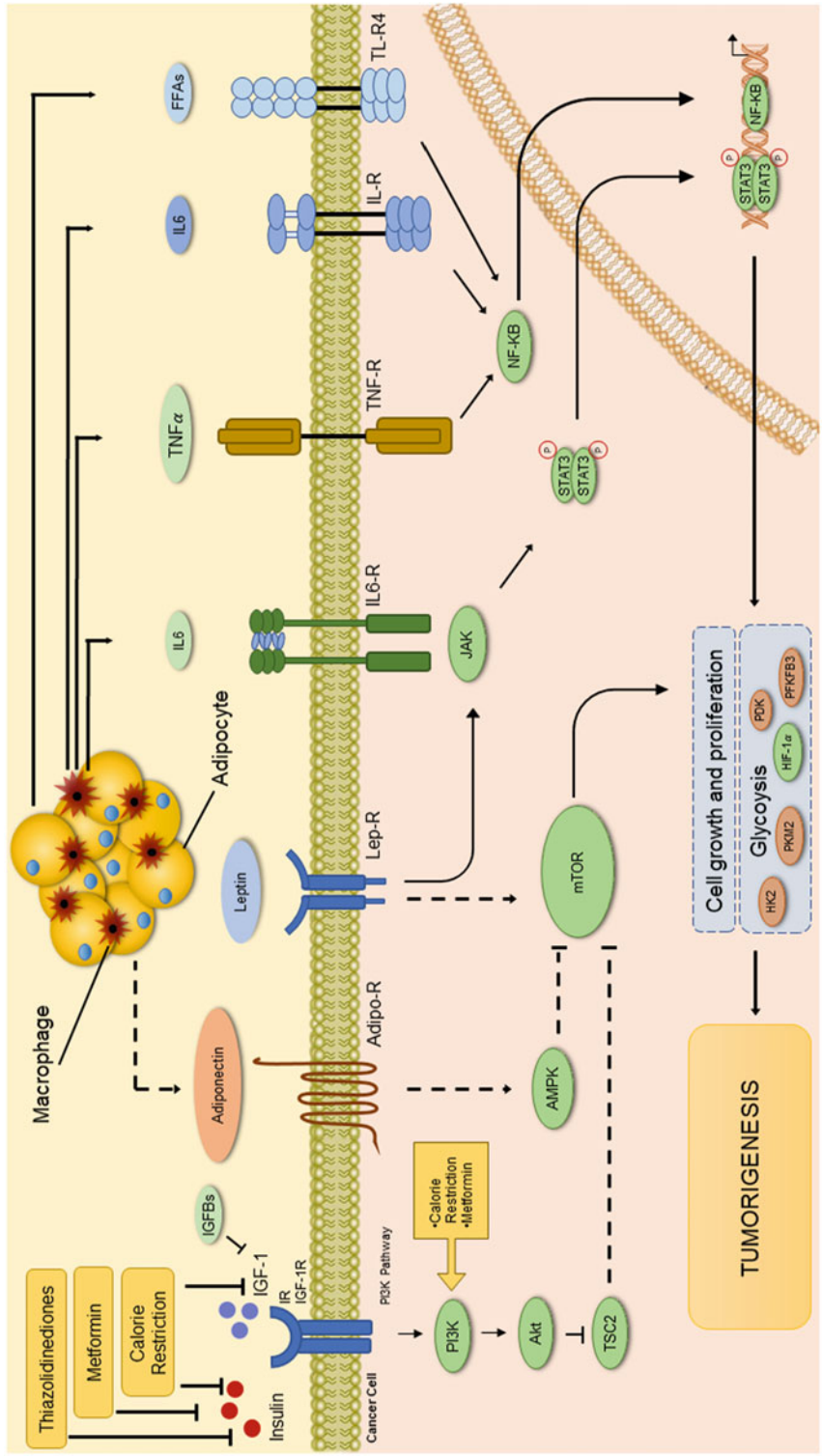

Fig. 28.1 Molecular pathways linking obesity and cancer. Insulin and insulin-like growth factor 1 (IGF-1) trigger off the phosphatidylinositol 3-kinase (PI3K) pathway, which in turn upregulates glycolysis and other metabolic pathways to generate energy needs for proliferation. Adipose tissue in the obese condition is a site of profound inflammatory activity using immune cells that secrete an abundance of cytokines that can influence on neighboring cancer cells to promote tumorigenesis through different metabolic levels.

pathway, alterations in adipokines pathophysiology, and subclinical chronic low-grade inflammation (Fig. 28.1).

Hyperinsulinemia/Insulin Resistance

Insulin resistance is a common feature of obese patients resulting in a compensatory increase in systemic insulin and IGF-1 levels (Ackerman et al. 2017). The excess of body weight is not the only parameter determining hyperinsulinemia: the distribution of the extra weight and of visceral adipose tissue is also a key variable. Hyperinsulinemia induces the production of IGF-1 by hepatocytes and downregulates the secretion of IGF-1 binding proteins (IGFBPs), resulting in an increase in bioavailable IGF-1. Several cancer cell types respond to insulin and IGF-1 receptor binding, by activating PI3K and MAPK pathways or other downstream networks, promoting cell survival, growth, and motility (Di Zazzo et al. 2014; Ackerman et al. 2017).

Insulin resistance, hyperinsulinemia, and high IGF-1 levels increase the risk of endometrial, breast, colorectal, and prostate cancer (Goodwin and Stambolic 2015). When colorectal cancer-susceptible mice were treated with an IGF-1-receptor inhibitor disrupting downstream signaling, tumor burden was significantly reduced (Ackerman et al. 2017).

In adipose tissue, insulin controls lipid storage and inhibition of lipolysis. Once glucose and insulin levels are elevated for prolonged periods as a consequence of overeating or lack of exercise, insulin can induce lipid storage in non-adipose tissue such as skeletal muscle. This inappropriate accumulation of intramuscular fatty acids contributes to altered insulin signaling.

Sex Hormones

Peripheral adipose tissue performs steroids aromatization: androgens and androgenic precursors are converted to estradiol by aromatase. In obesity, the excess of adipose tissue and the increased aromatase activity lead to a higher conversion rate, resulting in higher levels of circulating estrogens (Gérard and Brown 2018). In men and in postmenopausal women, the conversion of androgens to estrogens is dependent upon adipose tissue mass. Estrogen signaling has several consequences in tumor growth promotion. Indeed, estradiol is able to stimulate cell proliferation of breast epithelial and endometrial cells, to inhibit apoptosis, and to induce angiogenesis (Andò et al. 2019). Additionally, obesity is associated with lower plasma levels of sex hormone-binding globulin (SSBG), thus increasing bioavailable concentrations of estradiol and testosterone, resulting in a greater cancer risk (Di Zazzo et al. 2018).

Adipokines and Cancer

Adipokines are bioactive molecules released by WAT that acts locally in an autocrine and paracrine manner, but they also have a systemic, endocrine effect through blood circulation (Diedrich et al. 2015). Adipokines include adiponectin (APN), leptin, resistin, omentin, and chemerin; under physiological conditions, they regulate several processes such as energy balance, lipid metabolism, insulin sensitivity, inflammation, innate and adaptive immunity, angiogenesis, hematopoiesis, and cell proliferation (Schrover et al. 2016).

Abnormal accumulation of adipose tissue induces adipocyte dysfunctions, resulting into the alteration of its endocrine functions and consequently affecting the secretion of different adipokines, usually leading to increased leptin and decreased APN blood concentration. Abnormal adipokine secretion often represents a factor leading to cancer (Fig. 28.1) (Di Zazzo et al. 2019). Upon analysis of a panel of 14 obesity-related hormones, cytokines, coagulation factors, and other biomarkers, C-peptide, IL-6, and TNF-α pointed toward clear-cell renal carcinoma risk (Wang et al. 2019).

Adiponectin and Cancer

APN behaves as insulin-sensitizing, anti-apoptotic, and immune regulatory (Ackerman et al. 2017). Various homo-oligomers are recognized, and as adiposity accumulates, APN diminishes in the same proportion (Di Zazzo et al. 2019). APN usual receptors, AdipoR1 and AdipoR2, are physiologically highly relevant. Hexameric and multimeric APN binds to a different receptor, from the cadherin superfamily (Di Zazzo et al. 2019).

Signaling pathways for cellular responses include AMPK, mTOR, PI3K/AKT, MAPK, STAT3, and NF-kB, (Di Zazzo et al. 2019). AdipoR1 and AdipoR2 also impact energy balance, including insulin sensitization (Di Zazzo et al. 2019). Ceramidase stimulatory activity, which depletes intracellular ceramide, inhibits apoptosis (Holland et al. 2011).

Hypoadiponectinemia

Poor response to APN during excessive adiposity could be explained by low receptor values (Yamauchi et al. 2014). The same tends to occur during inflammation linked to diabetes and atherosclerosis (Di Zazzo et al. 2019). APN is usually classified as an anti-cancer molecule, with anti-inflammatory, anti-proliferative, and pro-apoptotic impact (Porcile et al. 2014; Di Zazzo et al. 2019).

Breast Cancer

Breast Cancer (BC) risk is heightened during advanced adiposity: (i) aromatization of androgens to estrogens stimulates growth of mammary cells; (ii) interference with APN physiology prevents its protective response (Avgerinos et al. 2019). Low APN levels are certainly deleterious in this context (Ye et al. 2014), including cancer growth and virulence. In the ERα-negative human BC cell line MDA-MB-231, Genes involved in cell cycle progression and apoptosis are one of the possible mechanisms (Mauro et al. 2014).

In an ERα-positive cell culture, APN leads to expression of ERα and cell growth (Mauro et al. 2014). Cross talk between APN/AdipoR1, IGF-IR, and ERα seems relevant (Mauro et al. 2015). Insulin and estrogen elevation, which favor cancer progression, contrast with depressed APN, including postmenopausal and ER-positive breast tumors (Di Zazzo et al. 2014; Mauro et al. 2014). APN modulates cell migration and invasion (Jia et al. 2014), AdipoR2 signals lymphatic and vascular penetration, and all of them are markers of metastatic disease (Jeong et al. 2011).

Gastrointestinal Malignancies

Strong correlation between obesity and the development of gastrointestinal (GI) cancers is reported (Murphy et al. 2018). The largest adipose intra-abdominal depot is the omentum, the so-called fatty apron connecting the stomach to the colon, enriched with immune cells and responsible for local inflammation. Obesity disrupts the homeostatic profiles of innate and adaptive immune cell populations within the omentum (O'Sullivan et al. 2018). APN plasma levels were found decreased in patients with GI cancers (Nagaraju et al. 2015). APN is suggested to be involved in esophageal mucosa remodeling, and it might have a protective role against cancer transformation, contributing to the link between obesity and lower esophageal carcinoma (EC) (Almers et al. 2015). Patients with metabolic syndrome, associated with increased leptin and decreased APN serum levels, are prone to Barrett's esophagus, a metaplastic change occurring in response to gastroesophageal reflux disease that can potentially lead to the EC. Moreover, high levels of LMW-APN are associated with a decreased risk of Barrett's esophagus (Tilg and Moschen 2014).

Beales and colleagues demonstrated that in OE33, an esophageal carcinoma cell line, leptin was able to induce proliferation, invasion, and migration and inhibit apoptosis in a STAT3-dependent manner and, by contrast, APN

inhibited leptin-stimulated proliferation *via* AdipoR1 (Beales et al. 2014). In gastric cancer, APN inhibited proliferation in *vitro* with most prominent effects in AZ521 and HGC27 gastric cell lines expressing high levels of AdipoR1/R2 mRNA. Moreover, higher concentrations of APN significantly reduce tumor volume and peritoneal metastases in *vivo* (Ishikawa et al. 2007), consistent with previous findings suggesting an anti-angiogenic and tumor suppressive role for this adipokine (Bråkenhielm et al. 2004). In the same models, APN elicits its biological effects through AdipoR1/R2 activation, whose expression was significantly associated with histological type and overall survival (Ishikawa et al. 2007). Negative AdipoR1 immunostaining was found in patients with lymphatic metastasis and peritoneal dissemination, while positive AdipoR1 expression corresponded to a longer survival rate (Tsukada et al. 2011).

Circulating APN levels have been also associated with increased risk of pancreatic cancer (Pothuraju et al. 2018). APN exerted its inhibitory effect through modulation of the β-catenin signaling pathway. In BxPC-3 and CFPAC-1, pancreatic cell lines both expressing the AdipoRs, APN reduced serum-induced phosphorylation of GSK-3β, decreased the nuclear accumulation of β-catenin, and downregulated the expression of cyclin D1. Knockdown of AdipoRs abolished the growth-inhibiting effect induced by APN in *vitro* and in xenograft models (Jiang et al. 2019).

Colorectal Cancer

Low APN is a marker of colorectal cancer (CRC) (Di Zazzo et al. 2019). Both AdipoR1 and AdipoR2 in turn could signal lymphatic metastasis (Ayyildiz et al. 2014), as well as (for AdipoR1) the ability to survive the illness (Choe et al. 2018). APN negatively controls CRC growth, by inhibiting the mechanistic target of rapamycin (mTOR) *via* AMPK phosphorylation, and decreasing PI3K and Akt phosphorylation (Parida et al. 2019).

In CRC models, APN knockdown resulted in increased multiplicity of aggressive colorectal polyps. In an APN-deficient mice model, APN treatment inhibited cancer progression and angiogenesis (Moon et al. 2013). APN deficiency also aggravated azoxymethane-induced colon cancer in C57BL/6J mice (Mutoh et al. 2011).

APN conferred protection against inflammation-induced colon cancers by preventing apoptosis in the goblet cells and promoting conversion of epithelial to goblet cells (Saxena et al. 2012). In HCT116, HT29, and LoVo CRC cell lines, APN induced G1/S cell cycle arrest with concomitant overexpression of p21 and p27 *via* AMPK phosphorylation; inhibition of AdipoRs released cells from APN-induced growth blockade (Kim et al. 2010). APN anticancer effect is glucose-dependent, possibly explaining why CRC survival is enhanced in a low glucose medium; however, the opposite occurs with APN in high glucose conditions (Habeeb et al. 2011).

Ovarian Cancer

Ovarian cancer patients have a lower blood concentration of APN than healthy women (Jin et al. 2016); low APN concentration was associated with longer progression-free survival times and a better tumor responsiveness to chemotherapy (Diaz et al. 2013; Slomian et al. 2019). In addition, AdipoR1 expression level in ovarian cancer tissues could represent a marker of prognosis, being positively associated with overall patient's survival (Li et al. 2017). Low APN plasma levels may favor ovarian cancer growth, induced by persistent activation of PI3K/Akt/mTOR signaling. Moreover, APN is able to repress human ovarian cancer cell growth and reverse the stimulatory effects of 17β-estradiol and IGF-1 on cell proliferation through the downregulation of their receptors (Hoffmann et al. 2018).

Endometrial Cancer

Low APN blood levels were associated with an increased risk and a worse prognosis of endometrial cancer (EMC). Low expression of AdipoR1

in endometrial cancer cells is associated with advanced tumor stage (Tumminia et al. 2019). Several hypotheses have been formulated the role of APN implying: (i) activation of AMPK (resulting in cell growth suppression and apoptosis); (ii) extracellular signal-regulated protein kinase (ERK) and Akt pathway inhibition; (iii) reduction of Cyclin D1 expression (Moon et al. 2011). Association seems more evident for type II EMC, and APN modulators are being explored for potential therapeutic avenues (Garikapati et al. 2019).

Prostate Cancer

Conflicting reports about APN exist (Hu et al. 2016). APN concentration in prostate cancer patients was low and connected to disease advent (Goktas et al. 2005). A lower AdipoR1 and AdipoR2 expression was observed in prostate neoplastic tissues compared with healthy prostate tissue (Michalakis et al. 2007). Growing evidence indicates that APN exerts an anti-proliferative action in prostate cancer cells, inhibiting dihydrotestosterone-activated cell proliferation (Bub et al. 2006). The ectopic overexpression of APN in prostate cancer cell lines inhibited mTOR-mediated neoplastic cell proliferation (Gao et al. 2015).

No links are also advocated (Baillargeon et al. 2006), or a significant positive correlation between APN concentrations and incidence of low- or intermediate-risk prostate cancer (Ikeda et al. 2015). Higher APN plasma levels were detected in subjects with cancer stage T3 (advanced) than in subjects with T2 (confined within the prostate). AdipoR2 findings could be a signal of cancer progression and metastasis (Rider et al. 2015).

Low Chronic Inflammation

Large adipocytes become distant from the blood supply, which can trigger chronic hypoxia and inflammation (Boutari and Mantzoros 2018).

Neutrophils and mast cells enhance inflammation whereas the opposite is expected from eosinophils and myeloid-derived suppressor cells. B- and T-lymphocytes and natural-killer cells are also engaged in the process, as well as M1 pro-inflammatory macrophages (ATMs) (Ouchi et al. 2011).

Macrophages constituting crown like structures elicit nuclear factor-kappa B (NF-κB) aggravating chronic inflammation (Ouchi et al. 2011). The cross talk between adipocytes and cancer engages IL-1, IL-6, and TNF-α, ROS generation, adipokines, and other molecules (Fig. 28.1) (Avgerinos et al. 2019). Cancer cells can also induce phenotype alteration of adjacent adipocytes, encompassing reduction of their lipid content and release of adipokine and matrix metalloproteinases (Dirat et al. 2011).

Inflammasome is an innate immune pathway activating proinflammatory cytokines, including IL-1 and IL-18 (Lamkanfi and Dixit 2014). Inflammasome-related genes are encountered in adipocytes (Yin et al. 2014), potentially stimulating cancer growth (Guo et al. 2016). Obesity treatment tends to ameliorate this negative profile (Hagman et al. 2017).

The Obesity Paradox in Cancer

Obesity negatively influences cancer recurrence, prognosis, and survival (Lennon et al. 2016). However, opposite evidence in certain circumstances suggests that obesity reduces cancer incidence and improves survival. Obesity has been ruled out as a risk for cancer mortality (Kuk et al. 2018). Body fatness reduced the nerve sheath tumor risk (Wiedmann et al. 2017); overweight or obesity attenuated mortality of bladder (Pavone et al. 2018); and lung cancer (Zhang et al. 2017) after surgery or chemotherapy. A meta-analysis also showed that obese patients with esophageal cancer had better long-term survival (Kayani et al. 2012).

The use of BMI as a measure of adiposity could partly explain the discrepancies, as it does not fully characterize the intricate biology and physiology of excess body fat. BMI cannot differentiate between lean mass and adipose tissue and depends upon gender, age, ethnicity, and race. Additionally, BMI does not estimate the

visceral adipose tissue (VAT), which seems to be metabolically more relevant. Computed tomography and MRI are better alternatives for quantification of VAT; however, they are not always feasible (Allott and Hursting 2015). Anthropometric measures, such as waist circumference (WC) and waist-to-hip ratio (WHR), are viable techniques (Sung et al. 2019), however, not perfect ones, as both VAT and subcutaneous abdominal tissue (SAT) are lumped together in the results (Avgerinos et al. 2019).

Obesity and Therapy

Obesity and comorbidities like dysglycemia, hypertension, and dyslipidemia could reduce the response to chemotherapy. Elevated BMI was associated with poor prognosis in patients affected by colon cancer who received surgical resection of primary tumor and adjuvant chemotherapy with capecitabine and oxaliplatin (Lashinger et al. 2014). In bevacizumab-treated metastatic CRC patients, high visceral fat and BMI were significantly associated with absence of a response and increased progression. BMI was negatively associated with response to standard first-line chemotherapy with platinum and taxanes in ovarian cancer patients (Califano et al. 2014). These results could be related to the expression by adipose tissue of angiogenic factors (in particular VEGF) (Ottaiano et al. 2018). Hyperinsulinemia, a known growth factor, could trigger chemoresistance to 5-fluorouracil, anthracyclines, taxanes, and other drugs upregulating P-glycoprotein (Wei et al. 2015).

Drug Dosage

Pharmacokinetic studies rarely address the obese. The most common strategy is dose-capping or dose-fixed regimens. The consequence of this "depotentiation" attitude may be the use of subtherapeutic strategies, conducting to disease recurrence and mortality. According to the American Society of Clinical Oncology, full weight should be adopted for dosage calculation.

Specific Cancer Therapies for Obese and Diabetic Patients?

A balanced and healthy diet may control factors that sustain obesity-related disease (i.e., IGF-1, insulin, leptin) (Avgerinos et al. 2019). In addition, vigorous aerobic exercise leads to a peak of circulating APN levels (Saunders et al. 2012). Moreover, there is an increasing interest in testing diabetes and cholesterol-lowering drugs for cancer therapy.

Metformin

Metformin could decrease incidence and mortality of cancer by inducing hepatic gluconeogenesis and reducing IR of peripheral tissues, resulting in lower insulin and IGF-1 levels (Gallagher and LeRoith 2015). Metformin blocks tumor growth and induces apoptosis through insulin-independent mechanisms (Safe et al. 2018). Furthermore, metformin decreases cancer recurrence by directly inducing cancer stem cell death (Gallagher and LeRoith 2015).

Glycemic control with metformin can restore adipokine concentrations, increasing APN, and decreasing pro-inflammatory adipokine levels in both humans and mice (Avgerinos et al. 2019). For prostate and breast malignancies, large meta-analyses failed to demonstrate benefits for metformin regarding cancer risk and mortality (Feng et al. 2019; Au Yeung and Schooling 2019; Wang et al. 2020). Yet in other contexts, such as rectal cancer treated by neoadjuvant chemoradiotherapy, better cancer response and lower risk of recurrence were elicited (Kim et al. 2020). Clinical trials are going on. Twelve of them address the following cancers: breast (five), along with head and neck, thyroid, endometrial, multiple myeloma, lymphocytic leukemia, and various gynecologic/ solid tumors (one of each) (www.cancer.gov, 2020).

Thiazolidinediones (TZDs) and Other Agents

Activation of PPAR-γ by TZDs could restrict cell proliferation by decreasing insulin concentration and also influencing key pathways of the Insulin/IGF-1 axis, such as MAPK, PI3K/mTOR, and Glycogen synthase kinase (GSK)3-β/Wnt/β-catenin cascades, which modulate cancer cell survival and differentiation. Additionally, the PPARγ agonists TZDs, rosiglitazone, and pioglitazone augment the circulating level of APN directly, enhancing its gene and protein expression in a dose-dependent manner (Parida et al. 2019). Yet, meta-analysis results are conflicting.

For bladder cancer, an increased risk with pioglitazone was announced, possibly dose and time dependent (Tang et al. 2018). As regards colorectal cancer, no advantages were detected with pioglitazone, whereas other PZDs seemed moderately protective (Liu et al. 2018). A lack of association with breast cancer risk is reported (Du et al. 2018). This last outcome is consistent with a meta-analysis addressing digestive cancers, in which the risk did not differ for incretin mimetics, insulin, metformin, sodium-glucose co-transporter 2, sulfonylureas, TZDs, alpha-glucosidase inhibitors, or placebo (Chai et al. 2019).

Therapies Targeting APN

Increasing plasma APN levels or mimicking some of its cancer-protective properties could mitigate the deleterious effects of metabolic dysfunctions on tumor development and progression (Vansaun 2013; Tumminia et al. 2019). Therefore, pharmacological increase in serum APN levels, up-regulation of AdipoRs expression, or synthesis of AdipoRs agonists could represent promising therapeutic strategies.

Using a high-throughput assay, several natural compounds showing AdipoRs agonist activity were identified. These compounds, acting preferably on AdipoR1 (e.g., matairesinol, arctiin, arctigenin, gramine) or AdipoR2 (e.g., syringin, parthenolide, taxifolion, deoxyschizandrin), shared important anti-cancer properties, including anti-proliferative and anti-inflammatory effects (Sun et al. 2013). ADP355, a peptide-based APN receptor agonist, prevented the proliferation of AdipoRs-positive cancer cell lines. ADP 355 showed high affinity with AdipoR1, and through the regulation of the canonical APN-regulated pathways (i.e., AMPK, Akt, STAT3, and ERK1/2), reduced breast tumor growth both *in vitro* and *in vivo* (Otvos Jr et al. 2015). Additionally, three peptides BHD1028, BHD43, and BHD44 have been designed to mimic APN actions. BHD1028 showed the highest affinity with AdipoR1 and the main activation of AMPK already at low concentration, more than ADP 355 (Kim et al. 2018).

Oral Adiponectin Receptor Agonist

AdipoRon (AdipoR) is the first oral AdipoRs agonist able to bind and activate AdipoR1 and AdipoR2 that successfully re-established APN functions, mainly activating AMPK and PPARγ pathways in obesity-related type 2 diabetes (Okada-Iwabu et al. 2013). Initial reports have also investigated the possible anti-cancer role of AdipoR in preclinical models, especially in pancreatic and ovarian cancer (Akimoto et al. 2018; Ramzan et al. 2019). However, modifying AdipoRs interactions could also result in infertility, cardiac damage, and reduced bone density (Holland and Scherer 2013).

Statins and Assorted Drugs

Statins have been reported to be effective in increasing circulating APN levels. Statins function by releasing cellular oxidative stress, resulting in increased APN multimerization and

secretion. Angiotensin converting enzyme inhibitors as well as angiotensin receptor antagonists Ramipril, Quinapril, Losartan, Telmisartan, Irbesartan, and Candesartan have similarly shown promising results in clinical trials. They function by enhancing APN secretion *via* PPARγ, though some of them are also known to induce transcription. Other potential drugs include non-statin anti-hyperlipidemic drugs like Fenofibrate and Zetia, non-TZD anti-diabetic drugs, such as Acarbose and the sulfonylurea Glimepiride and Sulfonylureas (Parida et al. 2019).

References

Ackerman SE, Blackburn OA, Marchildon F, Cohen P (2017) Insights into the Link Between Obesity and Cancer. Curr Obes Rep 6(2):195–203. https://doi.org/10.1007/s13679-017-0263-x

Akimoto M, Maruyama R, Kawabata Y, Tajima Y, Takenaga K (2018) Antidiabetic adiponectin receptor agonist AdipoRon suppresses tumour growth of pancreatic cancer by inducing RIPK1/ERK-dependent necroptosis. Cell Death Dis 9(8):804

Allott EH, Hursting SD (2015) Obesity and cancer: mechanistic insights from transdisciplinary studies. Endocr Relat Cancer 22:R365–R386. https://doi.org/10.1530/ERC-15-0400

Almers LM, Graham JE, Havel PJ, Corley DA (2015) Adiponectin may modify the risk of Barrett's Esophagus in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 13:2256–2264. https://doi.org/10.1016/j.cgh.2015.01.009

Andò S, Gelsomino L, Panza S, Giordano C, Bonofiglio D, Barone I, Catalano S (2019) Obesity, leptin and breast cancer: epidemiological evidence and proposed mechanisms. Cancers (Basel) 11(1):E62. https://doi.org/10.3390/cancers11010062

Au Yeung SL, Schooling CM (2019) Impact of glycemic traits, type 2 diabetes and metformin use on breast and prostate cancer risk: a Mendelian randomization study. BMJ Open Diabetes Res Care 7(1):e000872. https://doi.org/10.1136/bmjdrc-2019-000872

Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M (2019) Obesity and cancer risk: emerging biological mechanisms and perspectives. Metabolism 92:121–135. https://doi.org/10.1016/j.metabol.2018.11.001

Ayyildiz T, Dolar E, Ugras N, Adim SB, Yerci O (2014) Association of adiponectin receptor (Adipo-R1/-R2) expression and colorectal cancer. Asian Pac J Cancer Prev 15:9385–9390

Baillargeon J, Platz EA, Rose DP, Pollock BH, Ankerst DP, Haffner S, Higgins B, Lokshin A, Troyer D, Hernandez J et al (2006) Obesity, adipokines, and prostate cancer in a prospective population-based study. Cancer Epidemiol Biomark Prev 15:1331–1335

Beales ILP, Garcia-Morales C, Ogunwobi OO, Mutungi G (2014) Adiponectin inhibits leptin-induced oncogenic signalling in oesophageal cancer cells by activation of PTP1B. Mol Cell Endocrinol 382:150–158. https://doi.org/10.1016/j.mce.2013.08.013

Bifulco M, Ciaglia E (2017) Updates on "adiponcosis": More new incoming evidence strengthening the obesity-cancer link. Eur J Intern Med 41:e19–e20

Boutari C, Mantzoros CS (2018) Inflammation: a key player linking obesity with malignancies. Metabolism 81:A3–A6. https://doi.org/10.1016/j.metabol.2017.12.015

Bråkenhielm E, Veitonmäki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, Funahashi T, Cao Y (2004) Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci U S A 101:2476–2481

Bub JD, Miyazaki T, Iwamoto Y (2006) Adiponectin as a growth inhibitor in prostate cancer cells. Biochem Biophys Res Commun 340:1158–1166

Califano D, Pignata S, Losito NS, Ottaiano A, Greggi S, De Simone V, Cecere S, Aiello C, Esposito F, Fusco A, Chiappetta G (2014) High HMGA2 expression and high body mass index negatively affect the prognosis of patients with ovarian cancer. J Cell Physiol 229:53–59

Chai S, Yu S, Yang Z, Wu S, Gao L, Wang H, Zhang Y, Zhan S, Ji L, Sun F (2019) Effect of incretin-based therapies on cancers of digestive system among 101 595 patients with type 2 diabetes mellitus: a systematic review and network meta-analysis combining 84 trials with a median duration of 30 weeks. BMJ Open Diabetes Res Care 7(1):e000728. https://doi.org/10.1136/bmjdrc-2019-000728

Choe EK, Yi JW, Chai YJ, Park KJ (2018) Upregulation of the adipokine genes ADIPOR1 and SPP1 is related to poor survival outcomes in colorectal cancer. J Surg Oncol 117:1833–1840. https://doi.org/10.1002/jso.25078

Clinical Trials Using Metformin Hydrochloride (2020). www.cancer.gov/about-cancer/treatment/clinical-trials/intervention/metformin-hydrochloride. Accessed 17 March 2020

Coelho M, Oliveira T, Fernandes R (2013) Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci 9:191–200. https://doi.org/10.5114/aoms.2013.33181

Cozzo AJ, Fuller AM, Makowski L (2017) Contribution of adipose tissue to development of cancer. Compr Physiol 8:237–282. https://doi.org/10.1002/cphy.c170008

Di Zazzo E, Feola A, Zuchegna C, Romano A, Donini CF, Bartollino S, Costagliola C, Frunzio R, Laccetti P, Di Domenico M et al (2014) The p85 regulatory subunit of PI3K mediates cAMP-PKA and insulin biological effects on MCF-7 cell growth and motility. Sci World J 2014:565839

Di Zazzo E, Galasso G, Giovannelli P, Di Donato M, Castoria G (2018) Estrogens and their receptors in prostate cancer: therapeutic implications. Front Oncol 8:2. https://doi.org/10.3389/fonc.2018.00002

Di Zazzo E, Polito R, Bartollino S, Nigro E, Porcile C, Bianco A, Daniele A, Moncharmont B (2019) Adiponectin as link factor between adipose tissue and cancer. Int J Mol Sci 20:839

Diaz ES, Karlan BY, Li AJ (2013) Obesity-associated adipokines correlate with survival in epithelial ovarian cancer. Gynecol Oncol 129:353–357

Diedrich J, Gusky HC, Podgorski I (2015) Adipose tissue dysfunction and its effects on tumor metabolism. Horm Mol Biol Clin Invest 21:17–41. https://doi.org/10.1515/hmbci-2014-0045

Dirat B, Bochet L, Dabek M, Daviaud D, Dauvillier S, Majed B et al (2011) Cancer associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Res 71:2455–2465

Du R, Lin L, Cheng D, Xu Y, Xu M, Chen Y, Wang W, Bi Y, Li D, Lu J (2018) Thiazolidinedione therapy and breast cancer risk in diabetic women: a systematic review and meta-analysis. Diabetes Metab Res Rev 34(2). https://doi.org/10.1002/dmrr.2961

Feng Z, Zhou X, Liu N, Wang J, Chen X, Xu X (2019) Metformin use and prostate cancer risk: a meta-analysis of cohort studies. Medicine (Baltimore) 98 (12):e14955. https://doi.org/10.1097/MD.0000000000014955

Gallagher EJ, LeRoith D (2015) Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev 95:727–748

Gao Q, Zheng J, Yao X, Peng B (2015) Adiponectin inhibits VEGF-A in prostate cancer cells. Tumour Biol 36:4287–4292

Garikapati KK, Ammu VVVRK, Krishnamurthy PT, Chintamaneni PK, Pindiprolu SKSS (2019) Type-II endometrial cancer: role of adipokines. Arch Gynecol Obstet 300(2):239–249. https://doi.org/10.1007/s00404-019-05181-1

GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M et al (2017) Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 377:13–27

Gérard C, Brown KA (2018) Obesity and breast cancer—role of estrogens and the molecular underpinnings of aromatase regulation in breast adipose tissue. Mol Cell Endocrinol 466:15–30. https://doi.org/10.1016/j.mce.2017.09.014

Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju SN, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns BJ, Huxley R, Jackson CL et al (2016) Body-mass index and all-cause mortality: Individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 388:776–786

Goktas S, Yilmaz MI, Caglar K, Sonmez A, Kilic S, Bedir S (2005) Prostate cancer and adiponectin. Urology 65:1168–1172

Goodwin PJ, Stambolic V (2015) Impact of the obesity epidemic on cancer. Annu Rev Med 66:281–296

Guo B, Fu S, Zhang J, Liu B, Li Z (2016) Targeting inflammasome/IL-1 pathways for cancer immunotherapy. Sci Rep 6:36107

Habeeb BS, Kitayama J, Nagawa H (2011) Adiponectin supports cell survival in glucose deprivation through enhancement of autophagic response in colorectal cancer cells. Cancer Sci 102:999–1006

Hagman DK, Larson I, Kuzma JN, Cromer G, Makar K, Rubinow KB, Foster-Schubert KE, van Yserloo B, Billing PS, Landerholm RW, Crouthamel M, Flum DR, Cummings DE, Kratz M (2017) The short-term and long-term effects of bariatric/metabolic surgery on subcutaneous adipose tissue inflammation in humans. Metabolism 70:12–22. https://doi.org/10.1016/j.metabol.2017.01.030

Hoffmann M, Gogola J, Ptak A (2018) Adiponectin reverses the proliferative effects of estradiol and IGF-1 in human epithelial ovarian cancer cells by downregulating the expression of their receptors. Hormones Cancer 9:166–174

Holland WL, Scherer PE (2013) Cell biology. Ronning after the adiponectin receptors. Science 342:1460–1461. https://doi.org/10.1126/science.1249077

Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, Davis KE, Bikman BT, Halberg N, Rutkowski JM, Wade MR, Tenorio VM, Kuo MS, Brozinick JT, Zhang BB, Birnbaum MJ, Summers SA, Scherer PE (2011) Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nat Med 17:55–63

Hu MB, Xu H, Hu JM, Zhu WH, Yang T, Jiang HW, Ding Q (2016) Genetic polymorphisms in leptin, adiponectin and their receptors affect risk and aggressiveness of prostate cancer: evidence from a meta-analysis and pooled-review. Oncotarget 7:81049–81061

Ikeda A, Nakagawa T, Kawai K, Onozawa M, Hayashi T, Matsushita Y, Tsutsumi M, Kojima T, Miyazaki J, Nishiyama H (2015) Serum adiponectin concentration in 2,939 Japanese men undergoing screening for prostate cancer. Prostate Inte 3:87–92

Ishikawa M, Kitayama J, Yamauchi T, Kadowaki T, Maki T, Miyato H, Yamashita H, Nagawa H (2007) Adiponectin inhibits the growth and peritoneal metastasis of gastric cancer through its specific membrane receptors AdipoR1 and AdipoR2. Cancer Sci 98:1120–1127. https://doi.org/10.1111/j.1349-7006.2007.00486.x

Jeong YJ, Bong JG, Park SH, Choi JH, Oh HK (2011) Expression of leptin, leptin receptor, adiponectin and adiponectin receptor in ductal carcinoma in situ and invasive breast cancer. J Breast Cancer 14:96–103

Jia Z, Liu Y, Cui S (2014) Adiponectin induces breast cancer cell migration and growth factor expression. Cell Biochem Biophys 70:1239–1245

Jiang J, Fan Y, Zhang W, Shen Y, Liu T, Yao M, Gu J, Tu H, Gan Y (2019) Adiponectin suppresses human pancreatic cancer growth through attenuating the β-catenin signaling pathway. Int J Biol Sci 15:253–264. https://doi.org/10.7150/ijbs.27420

Jin JH, Kim HJ, Kim CY, Kim YH, Ju W, Kim SC (2016) Association of plasma adiponectin and leptin levels with the development and progression of ovarian cancer. Obstetrics Gynecol Sci 59:279–285

Kayani B, Okabayashi K, Ashrafian H, Harling L, Rao C, Darzi A, Kitagawa Y, Athanasiou T, Zacharakis E (2012) Does obesity affect outcomes in patients undergoing esophagectomy for cancer? A meta-analysis. World J Surg 36:1785–1795. https://doi.org/10.1007/s00268-012-1582-4

Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang SH, Kim SE, Lee GY, Lee JW, Jung SA et al (2010) Adiponectin represses colon cancer cell proliferation via AdipoR1-and-R2-mediated AMPK activation. Mol Endocrinol 24:1441–1452

Kim S, Lee Y, Kim JW, Son YJ, Ma MJ, Um JH, Kim ND, Min SH, Kim DI, Kim BB (2018) Discovery of a novel potent peptide agonist to adiponectin receptor 1. PLoS One 13:e0199256. https://doi.org/10.1371/journal.pone.0199256

Kim JM, Park JW, Lee JH, Park YH, Park SJ, Cheon JH, Kim WH, Kim TI (2020) Survival benefit for metformin through better tumor response by neoadjuvant CCRT in rectal cancer. Dis Colon Rectum. https://doi.org/10.1097/DCR.0000000000001624

Kuk JL, Rotondi M, Sui X, Blair SN, Ardern CI (2018) Individuals with obesity but no other metabolic risk factors are not at significantly elevated all-cause mortality risk in men and women. Clin Obes 8:305–312. https://doi.org/10.1111/cob.12263

Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H et al (2017) Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 356:j477

Lamkanfi M, Dixit VM (2014) Mechanisms and functions of inflammasomes. Cell 157:1013–1022

Lashinger LM, Rossi EL, Hursting SD (2014) Obesity and resistance to cancer chemotherapy: interacting roles of inflammation and metabolic dysregulation. Clin Pharmacol Ther 96:458–463

Lennon H, Sperrin M, Badrick E, Renehan AG (2016) The obesity paradox in cancer: a review. Curr Oncol Rep 18:56. https://doi.org/10.1007/s11912-016-0539-4

Li X, Yu Z, Fang L, Liu F, Jiang K (2017) Expression of adiponectin receptor-1 and prognosis of epithelial ovarian cancer patients. Med Sci Monit 23:1514–1521

Liu Y, Jin PP, Sun XC, Hu TT (2018) Thiazolidinediones and risk of colorectal cancer in patients with diabetes mellitus. Meta-Analysis 24(2):75–81. https://doi.org/10.4103/sjg.SJG_295_17

Mauro L, Pellegrino M, De Amicis F, Ricchio E, Giordano F, Rizza P, Catalano S, Bonofiglio D, Sisci D, Panno ML et al (2014) Evidences that estrogen receptor α interferes with adiponectin effects on breast cancer cell growth. Cell Cycle 13:553–564

Mauro L, Naimo GD, Ricchio E, Panno ML, Andò S (2015) Cross-talk between adiponectin and IGF-IR in breast cancer. Front Oncol 5:157

Michalakis K, Williams CJ, Mitsiades N, Blakeman J, Balafouta-Tselenis S, Giannopoulos A, Mantzoros CS (2007) Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: a case control study. Cancer Epidemiol Biomark Prev 16:308–313

Moon HS, Chamberland JP, Aronis K, Tseleni-Balafouta-S, Mantzoros CS (2011) Direct role of adiponectin and adiponectin receptors in endometrial cancer: in vitro and ex vivo studies in humans. Mol Cancer Ther 10:2234–2243

Moon HS, Liu X, Nagel JM, Chamberland JP, Diakopoulos KN, Brinkoetter MT, Hatziapostolou M, Wu Y, Robson SC, Iliopoulos D et al (2013) Salutary effects of adiponectin on colon cancer: in vivo and in vitro studies in mice. Gut 62:561–570

Murphy N, Jenab M, Gunter MJ (2018) Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. Nat Rev Gastroenterol Hepatol 15:659–670. https://doi.org/10.1038/s41575-018-0038-1

Mutoh M, Teraoka N, Takasu S, Takahashi M, Onuma K, Yamamoto M, Kubota N, Iseki T, Kadowaki T, Sugimura T et al (2011) Loss of adiponectin promotes intestinal carcinogenesis in min and wild-type mice. Gastroenterology 140:2000–2008

Nagaraju GP, Aliya S, Alese OB (2015) Role of adiponectin in obesity related gastrointestinal carcinogenesis. Cytokine Growth Factor Rev 26:83–93. https://doi.org/10.1016/j.cytogfr.2014.06.007

O'Sullivan J, Lysaght J, Donohoe CL, Reynolds JV (2018) Obesity and gastrointestinal cancer: the interrelationship of adipose and tumour microenvironments. Nat Rev Gastroenterol Hepatol 15:699–714. https://doi.org/10.1038/s41575-018-0069-7

Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, Yamaguchi M, Tanabe H, Kimura-Someya T, Shirouzu M, Ogata H, Tokuyama K, Ueki K, Nagano T, Tanaka A, Yokoyama S, Kadowaki T (2013) A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature 503:493–499. https://doi.org/10.1038/nature12656

Osborn O, Olefsky JM (2012) The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med 18:363–374. https://doi.org/10.1038/nm.2627

Ottaiano A, De Divitiis C, Capozzi M, Avallone A, Pisano C, Pignata S, Tafuto S (2018) Obesity and cancer: biological links and treatment implications.

Curr Cancer Drug Targets 18:231–238. https://doi.org/10.2174/1568009617666170330125619

Otvos L Jr, Kovalszky I, Olah J, Coroniti R, Knappe D, Nollmann FI, Hoffmann R, Wade JD, Lovas S, Surmacz E (2015) Optimization of adiponectin-derived peptides for inhibition of cancer cell growth and signaling. Pept Sci 104:156–166

Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11:85–97. https://doi.org/10.1038/nri2921

Parida S, Siddharth S, Sharma D (2019) Adiponectin, obesity, and cancer: clash of the bigwigs in health and disease. Int J Mol Sci 20:E2519. https://doi.org/10.3390/ijms20102519

Pavone C, Candela L, Fontana D, Simonato A (2018) Postoperative complications and 90-day mortality in radical cystectomy in high-risk patients: a monocentric retrospective observational study. Urologia 85:111–117. https://doi.org/10.1177/0391560317751600

Porcile C, Di Zazzo E, Monaco ML, D'Angelo G, Passarella D, Russo C, Di Costanzo A, Pattarozzi A, Gatti M, Bajetto A, Zona G, Barbieri F, Oriani G, Moncharmont B, Florio T, Daniele A (2014) Adiponectin as novel regulator of cell proliferation in human glioblastoma. J Cell Physiol 229:1444–1454. https://doi.org/10.1002/jcp.24582

Pothuraju R, Rachagani S, Junker WM, Chaudhary S, Saraswathi V, Kaur S, Batra SK (2018) Pancreatic cancer associated with obesity and diabetes: an alternative approach for its targeting. J Exp Clin Cancer Res 37:319. https://doi.org/10.1186/s13046-018-0963-4

Ramzan AA, Bitler BG, Hicdingks D et al (2019) Adiponectin receptor agonist AdipoRon induces apoptotic cell death and suppresses proliferation in human ovarian cancer cells. Mol Cell Biochem 461:37–46

Rider JR, Fiorentino M, Kelly R, Gerke T, Jordahl K, Sinnott JA, Giovannucci EL, Loda M, Mucci LA, Finn S et al (2015) Tumor expression of adiponectin receptor 2 and lethal prostate cancer. Carcinogenesis 36:639–647

Safe S, Nair V, Karki K (2018) Metformin-induced anticancer activities: recent insights. Biol Chem 399:321–335

Saunders TJ, Palombella A, McGuire KA, Janiszewski PM, Després JP, Ross R (2012) Acute exercise increases adiponectin levels in abdominally obese men. J Nutr Metab 2012:148729. https://doi.org/10.1155/2012/148729

Saxena A, Chumanevich A, Fletcher E, Larsen B, Lattwein K, Kaur K, Fayad R (2012) Adiponectin deficiency: role in chronic inflammation induced colon cancer. Biochim Biophys Acta Mol basis Dis 1822:527–536

Schrover IM, Spiering W, Leiner T, Visseren FL (2016) Adipose tissue dysfunction: clinical relevance and diagnostic possibilities. Horm Metab Res 48:213–225. https://doi.org/10.1055/s-0042-103243

Slomian GJ, Nowak D, Buczkowska M, Glogowska-Gruszka A, Slomian SP, Roczniak W, Janyga S, Nowak P (2019) The role of adiponectin and leptin in the treatment of ovarian cancer patients. Endokr Polska 70:57–63

Sun Y, Zang Z, Zhong L, Wu M, Su Q, Gao X, Zan W, Lin D, Zhao Y, Zhang Z (2013) Identification of adiponectin receptor agonist utilizing a fluorescence polarization based high throughput assay. PLoS One 8:e63354. https://doi.org/10.1371/journal.pone.0063354

Sung H, Siegel RL, Torre LA, Pearson-Stuttard J, Islami F, Fedewa SA, Goding Sauer A, Shuval K, Gapstur SM, Jacobs EJ, Giovannucci EL, Jemal A (2019) Global patterns in excess body weight and the associated cancer burden. CA Cancer J Clin 69:88–112. https://doi.org/10.3322/caac.21499

Tang H, Shi W, Fu S, Wang T, Zhai S, Song Y, Han J (2018) Pioglitazone and bladder cancer risk: a systematic review and meta-analysis. Cancer Med 7(4):1070–1080. https://doi.org/10.1002/cam4.1354

Tilg H, Moschen AR (2014) Mechanisms behind the link between obesity and gastrointestinal cancers. Best Pract Res Clin Gastroenterol 28:599–610. https://doi.org/10.1016/j.bpg.2014.07.006

Tsukada T, Fushida S, Harada S, Terai S, Yagi Y, Kinoshita J, Oyama K, Tajima H, Fujita H, Ninomiya I, Fujimura T, Ohta T (2011) Adiponectin receptor-1 expression is associated with good prognosis in gastric cancer. J Exp Clin Cancer Res 30:107. https://doi.org/10.1186/1756-9966-30-107

Tumminia A, Vinciguerra F, Parisi M, Graziano M, Sciacca L, Baratta R, Frittitta L (2019) Adipose tissue, obesity and adiponectin: role in endocrine cancer risk. Int J Mol Sci 20:E2863. https://doi.org/10.3390/ijms20122863

Vansaun MN (2013) Molecular pathways: adiponectin and leptin signaling in cancer. Clin Cancer Res 19:1926–1932

Wang Q, Tu H, Zhu M, Liang D, Ye Y, Chang DW, Long Y, Wu X (2019) Circulating obesity-driven biomarkers are associated with risk of clear cell renal cell carcinoma: a two-stage, case-control study. Carcinogenesis 40:1191–1197

Wang Y, Liu X, Yan P, Tang J, Chen T, Sun Y, Zhou W, Bi Y, Zhang ZJ (2020) Effect of metformin on the risk of prostate cancer in patients with type 2 diabetes by considering different confounding factors: a meta-analysis of observational studies. Eur J Cancer Prev 29(1):42–52. https://doi.org/10.1097/CEJ.0000000000000514

Wei Z, Liang L, Junsong L, Rui C, Shuai C, Guanglin Q, Shicai H, Zexing W, Jin W, Xiangming C, Shufeng W (2015) The impact of insulin on chemotherapeutic sensitivity to 5-fluorouracil in gastric cancer cell lines SGC7901, MKN45 and MKN28. J Exp Clin Cancer Res 34:64

Wiedmann MKH, Brunborg C, Di Ieva A, Lindemann K, Johannesen TB, Vatten L, Helseth E, Zwart JA (2017) Overweight, obesity and height as risk factors for meningioma, glioma, pituitary adenoma and nerve sheath tumor: a large population-based prospective cohort study. Acta Oncol 56:1302–1309. https://doi.org/10.1080/0284186X.2017.1330554

Yamauchi T, Iwabu M, Okada-Iwabu M, Kadowaki T (2014) Adiponectin receptors: a review of their structure, function and how they work. Best Pract Res Clin Endocrinol Metab 28:15–23

Ye J, Jia J, Dong S, Zhang C, Yu S, Li L, Mao C, Wang D, Chen J, Yuan G (2014) Circulating adiponectin levels and the risk of breast cancer: a meta-analysis. Eur J Cancer Prev 23:158–165

Yin Z, Deng T, Peterson LE, Yu R, Lin J, Hamilton DJ, Reardon PR, Sherman V, Winnier GE, Zhan M et al (2014) Transcriptome analysis of human adipocytes implicates the NOD-like receptor pathway in obesity-induced adipose inflammation. Mol Cell Endocrinol 394:80–87

Zhang X, Liu Y, Shao H, Zheng X (2017) Obesity paradox in lung cancer prognosis: evolving biological insights and clinical implications. J Thorac Oncol 12:1478–1488. https://doi.org/10.1016/j.jtho.2017.07.022